Exhibit 93, part 2

although another major pathway for the uptake of As^{III} and MMA^{III} (see below) is probably via hexose permeases (Rosen & Liu, 2009). Because As^{V} is rapidly reduced to As^{III} once it enters the cell (Carter *et al.*, 2003), the faster rate of cellular uptake of As^{III}, compared with As^{V}, may be part of the explanation for the greater toxicity of As^{III} (Bertolero *et al.*, 1987; Dopp *et al.*, 2004). However, the much higher chemical reactivity of As^{III}, compared to that of As^{V} is the major explanation. Some data suggests that glyceraldehyde 3-phosphate dehydrogenase (GAPDH) functions as a cytosolic As^{V} reductase *in vivo* (Németi *et al.*, 2006), although there are other candidate enzymes for this reaction (Aposhian *et al.*, 2004). As^{III} can react with cellular glutathione (GSH), either spontaneously or enzymatically, to form the tri-glutathione complex $As(SG)_3$ (Leslie *et al.*, 2004; Rey *et al.*, 2004).

As^{III} is metabolized by stepwise methylation, mainly in the liver. Although some details of inorganic arsenic metabolism remain uncertain (Aposhian & Aposhian, 2006), it is clear that the enzyme arsenic (+3 oxidation state) methyltransferase (AS3MT) is involved (Thomas *et al.*, 2007). Two schemes have been proposed for the methylation.

Reduction: As^{V} + thiol → As^{III}
Oxidative methylation: As^{III} + SAM → monomethylarsonate (MMA^{V})
Reduction: MMA^{V} + thiol → MMA^{III}
Oxidative methylation: MMA^{III} + SAM → dimethylAs^{V} (DMA^{V})
Reduction: DMA^{V} + thiol → DMA^{III}

Scheme 1: Inorganic arsenic metabolic pathway in mammals. As^{III} methylation is catalysed by AS3MT using *S*-adenosylmethionine (SAM) as a methyl donor and thioredoxin (or, less efficiently, other thiols such as glutaredoxin or lipoic acid) as a reductant. MMA^{III}: monomethylarsonous acid; MMA^{v}: monomethylarsonic acid; DMA^{III}: dimethylarsinous acid; DMA^{v}: dimethylarsinic acid

$As(SG)_3$ + SAM → $MMA^{III}(SG)_2$
$MMA^{III}(SG)_2$ + SAM → $DMA^{III}(SG)$

Scheme 2: The use of $As(SG)_3$ (tri-glutathione complex) as a substrate for methylation (Hayakawa *et al.*, 2005). Each of the glutathione (GSH) complexes can also decompose to yield GSH and MMA^{III} or DMA^{III}, which can then form MMA^{V} and DMA^{V}, respectively.

Neither reaction scheme necessarily goes to completion *in vivo*.

Evidence shows that exposure to arsine gas (AsH_3) results in the same metabolites as described above, but arsenobetaine found in seafood does not get metabolized in humans (Crecelius, 1977; Luten *et al.*, 1982; Le *et al.*, 1993, 1994; Buchet *et al.*, 1996; Schmeisser *et al.*, 2006). Information is not currently available on the other organo-arsenic compounds in seafood (Lai *et al.*, 2004).

Dimethylthioarsinic acid ($DMMTA^{V}$) and dimethyldithioarsinic acid ($DMDTA^{V}$) can be formed from DMA^{III} in red blood cells, and possibly in other cells (Naranmandura *et al.*, 2007; Suzuki *et al.*, 2007). These compounds have been observed in the urine of arsenic-exposed individuals (Raml *et al.*, 2007). They may have been misidentified as MMA^{III} and DMA^{III} in most studies (Hansen *et al.*, 2004).

Most organisms detoxify inorganic arsenic by cellular efflux (Rosen & Liu, 2009). In fibroblasts and other non-methylating cells, protection against arsenic takes place by specific mechanisms for $As(SG)_3$ efflux catalysed by multidrug-resistance-associated protein-transport ATPases MRP1 and MRP2, and maybe others (Kala *et al.*, 2000; Leslie *et al.*, 2004). These efflux pumps may also remove methylated arsenic–glutathione (As–GSH) complexes.

The rat is not a good model for the human in studying the toxicokinetics of arsenic because rat haemoglobin has a much higher affinity for trivalent arsenic species compared with human haemoglobin (Lu *et al.*, 2004). In mice, chronic

exposure (12 weeks) to As^V via drinking-water led to total tissue arsenic accumulation in the following ranking: kidney > lung > bladder > > > skin > blood > liver (Kenyon *et al.*, 2008). Monomethylated arsenic species (MMAs) predominated in the kidney, and dimethylated arsenic species (DMAs) predominated in the lung. Urinary bladder and skin had about equal ratios of inorganic arsenic and DMAs. The proportions of different arsenic species in urinary bladder tissue did not match those in urine.

In a study of intratracheal instillation of gallium arsenide, although substantial levels of arsenic were detected in blood and urine, no gallium was detected except for the amount that was left in the lung (Carter *et al.*, 2003).

Human exposure to arsenic is mainly via drinking-water. Trivalent arsenicals are eliminated via the bile, and pentavalent arsenicals are mainly eliminated by urinary excretion (Gregus *et al.*, 2000; Kala *et al.*, 2000; Csanaky & Gregus, 2002). Most population groups exposed mainly via drinking-water excrete 60–70% DMAs and 10–20% MMAs, the remainder 10–30% being inorganic compounds (Vahter, 2000). [The Working Group noted that this study did not include thiolated compounds, which had not yet been discovered.] Interindividual differences in methylation patterns may reflect genetic polymorphisms in AS3MT, and/or variability in the activities of different reductants (Thomas *et al.*, 2007).

4.2 Genetic and related effects

Arsenicals do not react directly with DNA, but cells treated with low concentrations of trivalent arsenicals show increased oxidative DNA damage (Wang *et al.*, 2002; Schwerdtle *et al.*, 2003; Shi *et al.*, 2004; Ding *et al.*, 2005; Wang *et al.*, 2007a). As^{III} and MMA^{III} are equally potent inducers of oxidative DNA damage in human urothelial cells, where they are equally toxic (Wang *et al.*, 2007a). Cytotoxic concentrations of trivalent arsenicals also cause DNA strand breaks and/or alkali-labile sites (Kligerman *et al.*, 2003; Klein *et al.*, 2007). In mice, DMA^V causes lung-specific DNA damage attributed to the DMA peroxy radical $(CH_3)_2AsOO$ (Yamanaka & Okada, 1994), which can also induce DNA strand breaks and DNA–protein crosslinks in cultured cells (Tezuka *et al.*, 1993).

Gallium arsenide and other arsenicals are not mutagenic in the Ames test (NTP, 2000; IARC, 2004). There was no increase in frequency of micronucleated erythrocytes in mice exposed to gallium arsenide by inhalation for 14 weeks (NTP, 2000).

Despite the fact that low (non-toxic) concentrations of trivalent arsenicals cause oxidative DNA damage such as 8-hydroxy-2′-deoxyguanosine, which is expected to cause G→T transversions, neither As^{III}, MMA^{III} nor DMA^{III} are significant point mutagens (Rossman, 2003; Klein *et al.*, 2007). This may be due to the efficient removal of oxidative DNA lesions (Fung *et al.*, 2007; Pu *et al.*, 2007b). At toxic concentrations, As^{III} increased large-deletion mutations in human/hamster hybrid cells through a mechanism mediated by reactive oxygen species (Hei *et al.*, 1998). MMA^{III} and DMA^{III} are weakly mutagenic in mouse lymphoma L5178Y cells, but only at toxic concentrations, and yield mostly deletions (Moore *et al.*, 1997; Kligerman *et al.*, 2003).

Using a transgenic cell line that readily detects deletions as well as point mutations, statistically significant mutagenesis was never observed for DMA^{III}, and was only seen for As^{III} or MMA^{III} at toxic concentrations. MMA^{III} yielded a mutant fraction about 4-fold over background at 11% survival, and 79% of these mutants were deletions (Klein *et al.*, 2007).

As^{III}, MMA^{III}, and DMA^{III} can induce chromosomal aberrations *in vitro* (Oya-Ohta *et al.*, 1996; Kligerman *et al.*, 2003). Statistically significant increases in chromosomal aberrations occur only at toxic doses (Klein *et al.*, 2007), except as a secondary effect of genomic

instability in long-term, low-dose treatment protocols (Sciandrello *et al.*, 2004). An analysis of micronuclei induced by As^{III} in human fibroblasts shows that at lower (relatively non-toxic) doses, As^{III} acts as an aneugen by interfering with spindle function and causing micronuclei with centromeres, but at high (toxic) doses, it acts as a clastogen, inducing micronuclei without centromeres (Yih & Lee, 1999). Aneuploidy is seen after treatment with As^{III} concentrations lower than those that cause chromosomal aberrations (Yih & Lee, 1999; Ochi *et al.*, 2004; Sciandrello *et al.*, 2002, 2004). Aneuploidy associated with disruption of spindle tubulin has been reported in other cells treated with arsenicals (Huang & Lee, 1998; Kligerman & Tennant, 2007; Ramírez *et al.*, 2007). Disrupted mitotic spindles and induced persistent aneuploidy were maintained even 5 days after As^{III} removal (Sciandrello *et al.*, 2002). Humans exposed to high concentrations of inorganic arsenic in drinking-water also show increased micronuclei in lymphocytes, exfoliated bladder epithelial cells and buccal mucosa cells, and sometimes chromosomal aberrations and sister chromatid exchange in whole-blood lymphocyte cultures (Basu *et al.*, 2001). Micronuclei and chromosomal aberrations are also induced in mice after intraperitoneal treatment with As^{III} (IARC, 2004).

Long-term low-dose treatment of human osteosarcoma cells with As^{III} (but not MMA^{III}) resulted in increased mutagenesis and transformation as a secondary effect of genomic instability (Mure *et al.*, 2003). In Chinese hamster V79–13 cells grown in the presence of low concentrations of As^{III}, genomic instability (measured by chromosomal aberrations in later generations) followed earlier changes in DNA methylation and aneuploidy (Sciandrello *et al.*, 2002, 2004). Other studies report gene amplification (Lee *et al.*, 1988; Rossman & Wolosin, 1992), and changes in gene expression, e.g. by DNA methylation changes (Liu *et al.*, 2006b; Klein *et al.*, 2007; Reichard *et al.*, 2007; Liu & Waalkes, 2008). Alterations of DNA methylation, along with histone modification, were seen in cells treated with As^{III} and MMA^{III} (Jensen *et al.*, 2008; Zhou *et al.*, 2008). Global DNA hypomethylation, along with hypermethylation of specific genes, was demonstrated in several As^{III}-transformed cells (Benbrahim-Tallaa *et al.*, 2005a; Liu & Waalkes, 2008). Oxidative damage to DNA has been shown to cause changes in DNA methylation (Cerda & Weitzman, 1997), suggesting a mechanism by which As^{III} may induce this effect. Changes in DNA methylation patterns could also result from altered SAM pools or downregulation of DNA methyltransferases (Hamadeh *et al.*, 2002; Benbrahim-Tallaa *et al.*, 2005a; Reichard *et al.*, 2007; Liu & Waalkes, 2008). Altered DNA methylation has also been observed in arsenic-exposed humans (Chanda *et al.*, 2006; Marsit *et al.*, 2006).

Although not a mutagen, As^{III} can enhance the mutagenicity of other agents (Rossman, 2003; Danaee *et al.*, 2004; Fischer *et al.*, 2005). Co-mutagenesis may occur by interference with both nucleotide-excision repair and base-excision repair (Hartwig *et al.*, 2002; Rossman, 2003; Danaee *et al.*, 2004; Wu *et al.*, 2005; Shen *et al.*, 2008). Nucleotide-excision repair was blocked in human fibroblasts with the following potency: $MMA^{III} > DMA^{III} > As^{III}$ (Shen *et al.*, 2008). As^{III} is not a very effective inhibitor of DNA-repair enzymes (Snow *et al.*, 2005). Rather, it appears to affect DNA-damage signalling events that control DNA repair. One of these is poly(ADP-ribose) polymerase (PARP) (Hartwig *et al.*, 2003; Qin *et al.*, 2008). PARP-1, the major PARP, is involved in base-excision repair by interacting with DNA-repair protein XRCC1, DNA polymerase β, and DNA ligase ^{III}. This might explain the inhibition of the ligation step of base-excision repair by As^{III} (Li & Rossman, 1989). MMA^{III} and DMA^{III} are more effective PARP inhibitors than is As^{III} (Walter *et al.*, 2007). The inhibition of PARP (and other proteins such as XPA) may be

mediated by the displacement of zinc (Zn) at Zn fingers (Schwerdtle *et al.*, 2003; Qin *et al.*, 2008).

Another important signal pathway affected by As^{III} is that mediated by tumour-suppressor gene *Tp53*. As^{III} was shown to prevent the activation of the P53 protein and the downstream expression of p21 after genotoxic insult (Vogt & Rossman, 2001; Tang *et al.*, 2006; Shen *et al.*, 2008). This has the effect of overriding the growth arrest at G1 (normally an opportunity for DNA repair to take place before DNA replication) in cells with DNA damage, and might explain part of the co-mutagenic effect (Vogt & Rossman, 2001; Hartwig *et al.*, 2002; Mudipalli *et al.*, 2005). p53 is also required for proficient global nucleotide-excision repair (Ferguson & Oh, 2005). The inhibition of thioredoxin reductase by As^{III}, MMA^{III} and DMA^{III} (Lin *et al.*, 1999) would cause the accumulation of oxidized thioredoxin, which may be partially responsible for p53 malfunction, as is shown in yeast (Merwin *et al.*, 2002). The upregulation of positive growth genes such as cyclin D by low concentrations of As^{III} would also tend to drive cells to cycle inappropriately (Trouba *et al.*, 2000; Vogt & Rossman, 2001; Luster & Simeonova, 2004).

In addition to inhibiting particular proteins, As^{III} (at slightly toxic concentrations) can down-regulate expression of some DNA repair genes (Hamadeh *et al.*, 2002; Andrew *et al.*, 2006; Sykora & Snow, 2008). However, very low, non-toxic concentrations, may have the opposite effect of upregulating DNA repair, concomitant with antioxidant defenses (Snow *et al.*, 2005; Sykora & Snow, 2008).

4.3 Co-carcinogenic and *in utero* carcinogenic effects

There are several non-genotoxic actions of As^{III} (sometimes demonstrated also for its trivalent metabolites) that may contribute to arsenic-induced carcinogenesis. The effects of As^{III} on preventing blockage of the cell cycle after genotoxic insult by a second agent were discussed above. In addition, low concentrations of As^{III} in the absence of a second agent can also stimulate cell proliferation *in vitro* (Germolec *et al.*, 1997; Trouba *et al.*, 2000; Vogt & Rossman, 2001; Benbrahim-Tallaa *et al.*, 2005b; Komissarova *et al.*, 2005), and *in vivo* (Germolec *et al.*, 1998; Burns *et al.*, 2004; Luster & Simeonova, 2004). The concentration-dependent increase in proliferation of human keratinocytes after 24 hours of treatment with arsenicals followed the potency trend: $DMA^{III} > MMA^{III} > As^{III}$ (Mudipalli *et al.*, 2005). As^{III} upregulates pro-growth proteins such as cyclin D1, c-myc, and E2F-1 (Trouba *et al.*, 2000; Vogt & Rossman, 2001; Ouyang *et al.*, 2007). The increased proliferation in mouse skin by As^{III} alone (in drinking-water) is not sufficient to induce skin cancer (Burns *et al.*, 2004), but may contribute to its co-carcinogenesis with solar ultraviolet. As^{III} was found to block the differentiation of skin cells, resulting in increased numbers of keratinocyte stem cells, the cells that proliferate (Patterson & Rice, 2007; Waalkes *et al.*, 2008). Because tumours may arise from stem cells, this would increase the pool of target cells for cancer of the skin.

Another mechanism for arsenic-related carcinogenesis might be acquired resistance to apoptosis. Long-term growth of human skin cells (HaCaT) in the presence of low concentrations of As^{III} resulted in cells with a generalized resistance to apoptosis (Pi *et al.*, 2005). This may allow the survival of cells with DNA damage, thus facilitating tumorigenesis. Even short-term exposure to As^{III} affected the apoptotic response to solar UV in a mouse keratinocyte cell line (Wu *et al.*, 2005) or to UVB in normal human keratinocytes (Chen *et al.*, 2005b). It is possible that the loss of the P53 function partially mediates the reduction in apoptotic response (Chen *et al.*, 2005b).

Numerous studies report increased inflammation after As^{III} exposure (NRC, 1999; Straub

et al., 2007). The transcription factor NF-κB is involved in the inflammatory response, and As^{III} causes oxidant-dependent activation of NF-κB (Barchowsky *et al.*, 1999). Activation of the NF-κB inflammatory signalling pathway was seen in infants born to As^{III}-exposed mothers in Bangladesh (Fry *et al.*, 2007).

As^{III} can disrupt the signalling of the estrogen receptor, glucocorticoid receptor, and of other steroids *in vivo* and *in vitro* (Benbrahim-Tallaa *et al.*, 2005b, 2007; Liu *et al.*, 2007; Davey *et al.*, 2008). Submicromolar concentrations of As^{III} stimulate the transcription of several steroid receptors, but slightly higher concentrations (1–3 μM) are inhibitory (Bodwell *et al.*, 2006). Exposure of mice *in utero* to As^{III} in a protocol leading to hepatocarcinogenesis resulted in altered expression of numerous genes involved in estrogen signalling or steroid metabolism, as well as hypomethylation of estrogen receptor α (Liu & Waalkes, 2008).

Angiogenesis, which provides a blood supply to developing tumours, is stimulated by very low concentrations of As^{III} (Mousa *et al.*, 2007; Straub *et al.*, 2007). This activity can be blocked by selenium compounds (Mousa *et al.*, 2007), which also blocks As^{III}-induced co-carcinogenesis with UV and delays mutagenesis (Uddin *et al.*, 2005).

Many of these effects depend on altered gene expression that can result from genetic and epigenetic effects discussed above. Changes in gene expression by As^{III} can also be mediated by the alteration of miRNA patterns (Marsit *et al.*, 2006). Some short-term changes in gene expression (e.g. changes in the expression of DNA-repair proteins or DNA methyltransferases) can result in long-term changes. Genome-wide changes in gene expression and signal transduction induced by arsenicals have been reported in several publications (Su *et al.*, 2006; Kumagai & Sumi, 2007; Ghosh *et al.*, 2008).

4.4 Synthesis

In the human body, inorganic arsenic compounds are converted to As^{III} and As^{V}. As^{V} is rapidly converted to As^{III}. As^{III} species are more toxic and bioactive than are As^{V} species, both because of the greater chemical reactivity of As^{III}, and because As^{III} enters cells more easily.

For inorganic arsenic and its metabolites, the evidence points to weak or non-existent direct mutagenesis, which is seen only at highly cytotoxic concentrations. On the other hand, long-term, low-dose exposure to inorganic arsenic – more relevant to human exposure – is likely to cause increased mutagenesis as a secondary effect of genomic instability, perhaps mediated by increased levels of reactive oxygen species, as well as co-mutagenesis with other agents. The major underlying mechanisms observed at low concentrations include the rapid induction of oxidative DNA damage and DNA-repair inhibition, and slower changes in DNA-methylation patterns, aneuploidy, and gene amplification. Gene amplification, altered DNA methylation, and aneuploidy lead to altered gene expression, and genomic instability. Inhibition of DNA repair leads to co-mutagenicity as well. These effects are consistent with the animal carcinogenicity data, in which As^{III} is a transgenerational carcinogen – with exposure being present during many cell generations – and in results observed in co-carcinogenicity studies.

For bladder tumours induced by high doses of DMA^{V} in the rat, the mechanism is likely to involve sustained cytotoxicity followed by stress-related cell proliferation, leading to genomic instability.

Inflammation and cytotoxicity may play a role in lung tumours induced by gallium arsenide in female rats.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of mixed exposure to inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate. Inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate, cause cancer of the lung, urinary bladder, and skin. Also, a positive association has been observed between exposure to arsenic and inorganic arsenic compounds and cancer of the kidney, liver, and prostate.

There is *sufficient evidence* in experimental animals for the carcinogenicity of dimethylarsinic acid, calcium arsenate, and sodium arsenite.

There is *limited evidence* in experimental animals for the carcinogenicity of sodium arsenate, gallium arsenide, arsenic trioxide, and trimethylarsine oxide.

There is *inadequate evidence* in experimental animals for the carcinogenicity of monomethylarsonic acid and arsenic trisulfide.

In view of the overall findings in animals, there is *sufficient evidence* in experimental animals for the carcinogenicity of inorganic arsenic compounds.

Arsenic and inorganic arsenic compounds are *carcinogenic to humans (Group 1).*

Dimethylarsinic acid and monomethylarsonic acid are *possibly carcinogenic to humans (Group 2B).*

Arsenobetaine and other organic arsenic compounds not metabolized in humans, are *not classifiable as to their carcinogenicity to humans (Group 3).*

The Working Group made the overall evaluation on 'arsenic and inorganic arsenic compounds' rather than on some individual arsenic compounds, based on the combined results of epidemiological studies, carcinogenicity studies in experimental animals, and data on the chemical characteristics, metabolism, and modes of action of carcinogenicity.

Elemental arsenic and inorganic arsenic species share the same metabolic pathway: arsenate→arsenite→methylarsonate→dimethylarsenite. Thus, independent of the mechanisms of the carcinogenic action, and independent of which of the metabolites is the actual ultimate carcinogen, different inorganic arsenic species should be considered as carcinogenic.

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BERYLLIUM AND BERYLLIUM COMPOUNDS

Beryllium and beryllium compounds were considered by previous IARC Working Groups in 1971, 1979, 1987, and 1993 (IARC, 1972, 1980, 1987, 1993). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms and molecular formulae for beryllium, beryllium–aluminium and beryllium–copper alloys, and certain beryllium compounds are presented in Table 1.1. The list is not exhaustive, nor does it comprise necessarily the most commercially important beryllium-containing substances; rather, it indicates the range of beryllium compounds available.

1.2 Chemical and physical properties of the agents

Beryllium (atomic number, 4; relative atomic mass, 9.01) is a metal, which belongs to Group IIA of the Periodic Table. The oxidation state of beryllium compounds is +2. Selected chemical and physical properties of beryllium, beryllium–aluminium and beryllium–copper alloys, and various beryllium compounds can be found in the previous *IARC Monograph* (IARC, 1993).

Beryllium is the lightest of all solid chemically stable substances, and has an unusually high melting-point. It has a very low density and a very high strength-to-weight ratio. Beryllium is lighter than aluminium but is greater than 40% more rigid than steel. It has excellent electrical and thermal conductivities. Its only markedly adverse feature is relatively pronounced brittleness, which restricts the use of metallic beryllium to specialized applications (WHO, 1990).

Because of its low atomic number, beryllium is very permeable to X-rays. Neutron emission after bombardment with α or γ rays is the most important of its nuclear physical properties, and beryllium can be used as a neutron source. Moreover, its low neutron absorptiveness and high-scattering cross-section make it a suitable moderator and reflector in structural materials in nuclear facilities; where most other metals absorb neutrons emitted during the fission of nuclear fuel, beryllium atoms only reduce the energy of such neutrons, and reflect them back into the fission zone (Ballance *et al.*, 1978; Newland, 1984; WHO, 1990).

The chemical properties of beryllium differ considerably from those of the other alkaline earths, but it has several chemical properties in common with aluminium. Like aluminium, beryllium is amphoteric and shows very high affinity for oxygen; on exposure to air or water vapour, a thin film of beryllium oxide forms on

Table 1.1 Chemical names (CAS names are in italics), CAS numbers, synonyms, and molecular formulae of beryllium and beryllium compounds

Chemical name	CAS Reg. No[a]	Synonyms	Formula
Beryllium metal	7440-41-7	*Beryllium*; beryllium element; beryllium metallic	Be
Beryllium–aluminum alloy[b]	12770-50-2	*Aluminium alloy, nonbase, Al,Be*; aluminium–beryllium alloy	Al.Be
Beryllium–copper alloy[c]	11133-98-5	*Copper alloy, base, Cu,Be*; copper–beryllium alloy	Be.Cu
Beryl	1302-52-9	Beryllium aluminosilicate; beryllium aluminium silicate	$Al_2Be_3(SiO_3)_6$
Beryllium chloride	7787-47-5	Beryllium dichloride	$BeCl_2$
Beryllium fluoride	7787-49-7 (12323-05-6)	Beryllium difluoride	BeF_2
Beryllium hydroxide	13327-32-7 (1304-49-0)	Beryllium dihydroxide	$Be(OH)_2$
Beryllium sulfate	13510-49-1	*Sulfuric acid, beryllium salt (1:1)*	$BeSO_4$
Beryllium sulfate tetrahydrate	7787-56-6	*Sulfuric acid, beryllium salt (1:1), tetrahydrate*	$BeSO_4.4H_2O$
Beryllium oxide	1304-56-9	Beryllia; beryllium monoxide	BeO
Beryllium carbonate basic[d]	1319-43-3	*Carbonic acid, beryllium salt, mixture with beryllium hydroxide (Be(OH)$_2$)*	$BeCO_3.Be(HO)_2$
Beryllium nitrate	13597-99-4	Beryllium dinitrate; *nitric acid, beryllium salt*	$Be(NO_3)_2$
Beryllium nitrate trihydrate	7787-55-5	*Nitric acid, beryllium salt, trihydrate*	$Be(NO_3)_2.3H_2O$
Beryllium nitrate tetrahydrate	13510-48-0	Beryllium dinitrate tetrahydrate; *nitric acid, beryllium salt, tetrahydrate*	$Be(NO_3)_2.4H_2O$
Beryllium phosphate	13598-15-7	*Phosphoric acid, beryllium salt (1:1)*	$BeHPO_4$
Beryllium silicate[e]	13598-00-0	Phenazite; *phenakite*	$Be_2(SiO_4)$
Zinc beryllium silicate	39413-47-3 (63089-82-7)	*Silicic acid, beryllium zinc salt*	Unspecified

[a] Replaced CAS Registry numbers are shown in parentheses.

[b] Related compound registered by CAS is beryllium alloy, base, Be, Al historically (Lockalloy), Al (24–44%).Be (56–76%) [12604-81-8; replaced Registry No., 12665-28-0]; 60 beryllium–aluminium alloys are registered with CAS numbers, with different percentages of the two elements.

[c] Related compound registered by CAS is beryllium alloy, base, Be,Cu [39348-30-6]; 111 beryllium–copper alloys are registered with CAS numbers, with different percentages of the two elements.

[d] CAS name and Registry number shown were selected as being closest to the formula given by Lide (1991). Related compounds registered by CAS are: bis[carbonato(2)]dihydroxytriberyllium, $(BeCO_3)2.Be(OH)_2$ [66104-24-3]; carbonic acid, beryllium salt (1:1), tetrahydrate, $BeCO_3.4H_2O$ [60883-64-9]; carbonic acid, beryllium salt (1:1), $BeCO_3$ [13106-47-3]; and bis[carbonato(2-)]oxodiberyllium, $(CO_3)2Be_2O$ [66104-25-4].

[e] Related compounds registered by CAS are: bertrandite, $Be_4(OH)_2O(SiO_3)_2$ [12161-82-9]; beryllium silicate, formula unspecified [58500-38-2]; silicic acid (H_2SiO_3), beryllium salt (1:1), $Be(SiO_3)$ [14902-94-4]; silicic acid (H_4SiO_4), beryllium salt (1:2), $Be_2(SiO_4)$ [15191-85-2]

the surface of the bare metal, rendering the metal highly resistant to corrosion, to hot and cold water, and to oxidizing acids (Newland, 1984; Petzow *et al.*, 1985; WHO, 1990).

1.3 Use of the agents

Beryllium is primarily used in its metallic form, in alloys, or in beryllium oxide ceramics. Its physical and mechanical properties make it useful for many applications across a range of industries. These properties include: outstanding strength (when alloyed), high melting-point,

high specific heat, excellent thermal properties, electrical conductivity, reflectivity, low neutron absorption, and high neutron-scattering cross-sections, and transparency to X-rays (WHO, 1990; USGS, 2007).

Industries using beryllium and beryllium products include: aerospace (e.g. altimeters, braking systems, engines, and precision tools), automotive (e.g. air-bag sensors, anti-lock brake systems, steering wheel connecting springs), biomedical (e.g. dental crowns, medical laser components, X-ray tube windows), defence (e.g. heat shields, missile guidance systems, nuclear reactor components), energy and electrical (e.g. heat exchanger tubes, microwave devices, relays and switches), fire prevention (e.g. non-sparking tools, sprinkler system springs), consumer products (e.g. camera shutters, computer disk drives, pen clips), manufacturing (e.g. plastic injection moulds), sporting goods (e.g. golf clubs, fishing rods, naturally occurring and man-made gemstones), scrap recovery and recycling, and telecommunications (e.g. mobile telephone components, electronic and electrical connectors, undersea repeater housings) (Kreiss *et al.*, 2007).

1.3.1 Beryllium metal

Some typical applications of beryllium metal include: aerospace technology (structural material, inertia guidance systems, additives in solid propellant rocket fuels, aircraft brakes, mirror components of satellite optical systems, gyroscopes), nuclear technology (moderator and reflector of neutrons in nuclear reactors, neutron source when bombarded with α particles), X-ray and radiation technology (special windows for X-ray tubes), computer technology and alloys (e.g. beryllium–copper alloys; hardening of copper, and developmental brass alloys) (WHO, 1990; Petzow *et al.*, 2007).

1.3.2 Beryllium-containing alloys

Approximately 75% of manufactured beryllium is used in alloys, 95% of which is copper alloy (Jakubowski & Palczynski, 2007). Because of the properties it confers on other metals (i.e. low density combined with strength, high melting-point, resistance to oxidation, and a high modulus of elasticity), beryllium alloys are light-weight materials that can withstand high acceleration and centrifugal forces (WHO, 1990). Beryllium–copper alloys are commonly used in the electronics (e.g. switch and relay blades, electronic connector contacts, control bearings, magnetic sensing device housings, and resistance welding systems), automotive (e.g. air-bag sensors), military (e.g. electro-targeting and infrared countermeasure devices, missile systems, advanced surveillance satellites, and radar systems), and aerospace industries (e.g. landing gear bearings, weather satellites). Other applications include computers, oil exploration equipment, medical appliances, sporting equipment (e.g. golf clubs), and non-sparking tools (e.g. in petroleum refineries) (WHO, 1990; Kaczynski, 2004; Jakubowski & Palczynski, 2007).

1.3.3 Beryllium oxide

The ceramic properties of sintered beryllium oxide make it suitable for the production or protection of materials to be used at high temperatures in corrosive environments. It is used in lasers and electronics (e.g. transistor mountings, semiconductor packages, microelectronic substrates, microwave devices, high-powered laser tubes), in aerospace and military applications (e.g. gyroscopes and armour), refractories (e.g. thermocouple sheaths and crucibles), nuclear technology (reactor fuels and moderators), and medical/dental applications (e.g. ceramic crowns). It is also used as an additive (to glass, ceramics, and plastics) in the preparation of beryllium compounds, and as a catalyst for organic reactions (WHO, 1990; Taylor *et al.*, 2003).

1.3.4 Other beryllium compounds

Other important beryllium compounds include the beryllium halides (beryllium chloride and beryllium fluoride), beryllium hydroxide, and beryllium sulfate. Beryllium chloride has been used as a raw material in the electrolytic production of beryllium, and as the starting material for the synthesis of organo-beryllium compounds (O'Neil, 2006; Petzow *et al.*, 2007). Beryllium fluoride is used as an intermediate in the preparation of beryllium and beryllium alloys. It is used in nuclear reactors and glass manufacture, and as an additive to welding and soldering fluxes (O'Neil, 2006; Petzow *et al.*, 2007). Beryllium hydroxide is used as an intermediate in the manufacture of beryllium and beryllium oxide (O'Neil, 2006). Beryllium sulfate tetrahydrate is used as an intermediate in the production of beryllium oxide powder for ceramics (Kaczynski, 2004).

1.4 Environmental occurrence

Beryllium occurs naturally in the earth's crust, and is released in the environment as a result of both natural and anthropogenic activities. The environmental occurrence of beryllium has been reviewed extensively (WHO, 1990; ATSDR, 2002; Taylor *et al.*, 2003).

1.4.1 Natural occurrence

The 44th most abundant element in the earth's crust, beryllium occurs in rocks and minerals (mica schist, granite, pegmatite, and argillite), although the most highly enriched beryllium deposits are found in granitic pegmatites, in which independent beryllium minerals crystallize. Some 50 beryllium-containing minerals have been identified. Only ores containing beryl ($3BeO.Al_2O_3.6SiO_2$) and bertrandite ($4BeO.2SiO_2.H_2O$) have achieved economic significance. The average terrestrial abundance of beryllium is 2–5.0 mg/kg. (IARC, 1993; Jakubowski & Palczynski, 2007; USGS, 2007).

1.4.2 Air

Beryllium particulates are released in the atmosphere from both natural and anthropogenic sources. Windblown dust is the most important natural source of atmospheric beryllium (approximately 95%), with volcanic activity accounting for the remainder. The major anthropogenic source of atmospheric beryllium is the combustion of coal and fuel oil. Other sources include: municipal waste incineration, beryllium alloy and chemical use (includes ore processing, production, use and recycling), and the burning of solid rocket fuel (WHO, 2001; ATSDR, 2002). Ambient concentrations of atmospheric beryllium are generally low. Based on measurements at 100 locations, an average daily concentration of less than 0.5 ng/m^3 was reported in the United States of America (Jakubowski & Palczynski, 2007). Atmospheric concentrations of beryllium in the vicinity of beryllium-processing plants are often higher than those measured elsewhere (IARC, 1993).

1.4.3 Water

Beryllium is released in the aquatic environment from both natural and anthropogenic sources. Weathering of beryllium-containing rocks and soils is the primary source of release, although leaching of coal piles may also contribute to beryllium entering surface water. Anthropogenic sources include industrial waste water effluents (e.g. from electric utility industries). The deposition of atmospheric fall-out (of anthropogenic and natural sources) is also a source of beryllium in surface waters. However, the relative importance of this contribution to aquatic concentrations of beryllium is difficult to assess (ATSDR, 2002).

Beryllium concentrations in surface waters are usually in the range of 0.01–0.1 µg/L (WHO, 1990). The concentration of beryllium in deep ocean waters tend to be fairly uniform worldwide,

and are estimated to be approximately three orders of magnitude lower than that of surface river water (Jakubowski & Palczynski, 2007). Beryllium concentrations in drinking-water are on average 0.19 µg/L, with a range of 0.01–1.22 µg/L (Kolanz, 2001).

1.5 Human exposure

1.5.1 Exposure of the general population

The primary route of beryllium exposure for the general population is via the ingestion of contaminated food or water. The daily intake of beryllium by non-occupationally exposed persons in the USA from drinking-water is estimated to be 1 µg per day (assuming an average concentration of 0.5 µg/L, and a drinking-water consumption rate of 2 L/day). In the 1980s, the Environmental Protection Agency in the USA estimated the daily intake of beryllium in food to be approximately 0.12 µg per day (based on an arbitrary value of 0.1 ng beryllium per gram of food, and an assumption that a normal adult consumes 1200 g of food per day). Other studies have estimated the daily intake of beryllium in food to be in the range of 5–100 µg per day (ATSDR, 2002).

The inhalation of beryllium via ambient air or smoking is considered to be a minor exposure route for the general population. Assuming an average airborne concentration of less than 0.03 ng/ m^3 beryllium per day, and a breathing rate of 20 m^3 of air per day, the estimated daily intake for an adult in the USA is approximately 0.6 ng of beryllium, or less, per day. This estimated intake is likely to be higher for for persons living near point sources of beryllium emission (ATSDR, 2002).

1.5.2 Occupational exposure

The occupational environment is the predominant source of beryllium exposure for humans. Inhalation of beryllium dust and dermal contact with beryllium-containing products are the main routes of occupational exposure, although there may be the potential for in-home exposure if contaminated work garments are worn at home (ATSDR, 2002; NTP, 2004). Industries using or producing beryllium include: aerospace; automotive; biomedical; defence; energy and electrical; fire prevention; instruments, equipment and objects; manufacturing; sporting goods and jewellery; scrap recovery and recycling; and telecommunications (Kreiss *et al.*, 2007).

Based on data obtained from the primary beryllium industry and government agencies, Henneberger *et al.* (2004) estimated that 134000 workers were potentially exposed to beryllium in the USA (1500 in the primary beryllium industry, 26500 in the Department of Energy or Department of Defence, and between 26400 and 106000 in the private sector, outside of the primary industry). This figure may be an underestimate because of the limited data on potential beryllium exposures in military and nuclear weapons workplaces, and in many others where beryllium is a minor or unsuspected component (e.g. aluminium smelting, scrap recovery, and electronics recycling). The number of workers in the USA ever exposed to beryllium is likely to be far higher than 134000, as it does not include approximately 250000 construction workers that are employed at nuclear weapons reclamation sites alone (Kreiss *et al.*, 2007).

Estimates of the number of workers potentially exposed to beryllium and beryllium compounds have been developed by CAREX in Europe. Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX (CARcinogen EXposure) database estimates that 66069 workers were exposed to beryllium and beryllium compounds in the European Union, with over 80% of workers employed in the manufacture of machinery, except electrical (n = 38543); manufacture of fabricated metal products except machinery and equipment (n = 5434); manufacture of electrical machinery,

apparatus and appliances (n = 4174); manufacture of professional, scientific, measuring and controlling equipment not elsewhere classified (n = 3708); and manufacture of transport equipment (n = 3328). CAREX Canada estimates that 4000 Canadians (86% male) are exposed to beryllium in their workplaces (CAREX Canada, 2011). These industries include: building equipment contractors, medical equipment and supplies manufacturing, residential building construction, motor vehicle parts manufacture, automotive repair and maintenance, non-residential building construction, commercial/industrial machinery repair and maintenance, architectural and structural metals manufacturing.

Data on early occupational exposures to beryllium were summarized in the previous *IARC Monograph* (IARC, 1993), and data from studies on beryllium exposure published since are summarized below.

(a) Processing and manufacturing

Sanderson *et al.* (2001a) investigated historical beryllium exposures in a beryllium-manufacturing plant in the USA during 1935–92 for the purpose of reconstructing exposures for an epidemiological study. Daily weighted average (DWA) exposure estimates ranged from 1.7–767 μg/m^3 for 1935–60; 1.0–69.9 μg/m^3 for 1961–70; 0.1–3.1 μg/m^3 for 1971–80; and 0.03–1.4 μg/m^3 for 1981–92 (range of geometric means).

Seiler *et al.* (1996a, b) investigated historical beryllium exposure data (n = 643) collected in five beryllium-processing facilities in the USA during 1950–75. Descriptive data for representative job titles in November 1974 indicated that DWA beryllium exposures ranged from a minimum of 0.3 μg/m^3 for a ceramics machine operator to a maximum of 111.4 μg/m^3 for a vacuum cast furnace operator. Approximately 73% of the maximum breathing zone DWA exposures exceeded the 2 μg/m^3 standard; only 18% of the general air DWA beryllium exposures exceeded the standard.

Deubner *et al.* (2001a) analysed 34307 airborne beryllium measurements (general air, breathing zone, and personal lapel) collected during 1970–99 at a beryllium mining and extraction facility in Delta, UT, USA, and compared them to a mixed beryllium products facility and a beryllium ceramics facility located in Elmore, OH and Tucson, AZ, respectively. DWAs (n = 1519) were calculated to estimate task-specific, time-weighted average (TWA) exposures for workers at the Delta facility. The general area and breathing zone sampling data indicated that average annual beryllium concentrations at the Delta plant declined over the study period. The range of annual median general area sample concentrations at the mining and milling plant was comparable to that at the beryllium ceramics facility (0.1–0.6 μg/m^3 versus 0.1–0.4 μg/m^3, respectively). These data were lower than those observed at the mixed beryllium products facility (range of annual median general area sample concentrations, 0.1–1.0 μg/m^3). At the mining and milling facility, the highest exposures were observed in jobs involving beryllium hydrolysis and wet-grinding activities. This observation was independent of the exposure assessment method used.

Kreiss *et al.* (1997) analysed 106218 airborne beryllium measurements collected during 1984–93 at a beryllium-manufacturing plant producing pure metal, oxide, alloys, and ceramics. Of these, 90232 were area samples (30-minute samples: n = 30872; full-shift, continuous samples: n = 59360), and 15986 were personal samples (1–15 minute breathing zone samples: n = 15787; full-shift personal lapel samples: n = 179). Using these data, DWA exposures were calculated for most jobs. Median area concentrations were 0.6 μg/m^3 and 0.4 μg/m^3 for full-shift and short-term samples, respectively. Median personal concentrations were 1.4 μg/m^3 and 1.0 μg/m^3 for short-term and full-shift samples, respectively. The highest median area concentrations were observed in the alloy arc furnace

and alloy melting-casting areas, and the highest median breathing zone concentrations were observed in the beryllium powder and laundry areas.

Kent *et al.* (2001) collected full-shift particle-size-specific personal samples (n = 53) and area samples (n = 55) in five furnace areas at a beryllium-manufacturing facility. Personal samples were collected with Anderson impactors and general area samples were collected with micro-orifice uniform deposit impactors (MOUDIs). The median total mass concentration of beryllium particles (in μg/m^3) was reported by work process area and particle size. Median personal aerosol concentrations ranged from 0.8–5.6 μg/m^3 for total particle mass, and 0.05–0.4 μg/m^3 for alveolar-deposited particle mass. Median area concentrations ranged from 0.1–0.3 μg/m^3 for total particle mass, and 0.02–0.06 μg/m^3 for alveolar-deposited particle mass.

(b) Beryllium oxide ceramics

As part of a study to examine the relationship between sensitization and beryllium exposure in a beryllium ceramics plant in the USA, Kreiss *et al.* (1996) reviewed all general area (n = 5664) and personal breathing zone (n = 4208) samples collected during 1981–92. Of the area samples collected, 14% (n = 774) were full-shift samples collected from 1983 onwards; of the personal breathing zone samples, 1.7% (n = 75) were full-shift samples collected from 1991 onwards. Using average general area, full-shift area and breathing zone measurements, DWA exposures for most occupations were calculated. Of the full-shift area samples, 76% were reported to be at or below the detection limit of 0.1 μg/m^3. The median general area concentration was at or below the detection limit, with measured concentrations ranging as high as 488.7 μg/m^3. Median personal breathing zone concentrations were 0.3 μg/m^3 (maximum, 1931 μg/m^3) and 0.20 μg/m^3 (range, 0.1–1.8 μg/m^3) for the short-term and full-shift samples, respectively. Machinists were observed to have the highest exposures, with breathing zone concentrations of 63.7 μg/m^3, and a median DWA exposure of 0.9 μg/m^3.

Henneberger *et al.* (2001) conducted a follow-up to the Kreiss *et al.* (1996) study, screening workers at a US beryllium ceramics plant to determine whether the plant-wide prevalence of beryllium sensitization and disease had declined in the 6-year interval since first screening, and to explore exposure–response relationships. Historical airborne beryllium measurements (task- and time-specific) were combined with individual work histories to compute worker-specific beryllium exposures (mean, cumulative, and peak). A total of 18903 beryllium measurements were collected during 1981–98, of which 43% were short-term (1–15 minute), task-specific personal breathing zone samples, and 57% were short-term (30 minute) general area samples. Mean calculated exposures for all workers ranged from 0.05 μg/m^3 (i.e. less than the limit of detection) to 4.4 μg/m^3. When duration of employment was taken into account, short-term workers (i.e. those hired since the previous survey) had lower mean (median value: 0.28 μg/m^3 versus 0.39 μg/m^3) and peak concentrations (median value: 6.1 μg/m^3 versus 14.9 μg/m^3) than long-term workers.

Cummings *et al.* (2007) conducted a follow-up study in the same beryllium oxide ceramics manufacturing facility considered by Henneberger *et al.* (2001) to assess the effectiveness of an enhanced preventive programme to reduce beryllium sensitization. Sensitization for newly hired workers was compared with that for workers hired from 1993–98, and tested in the 1998 survey. Full-shift personal exposure data collected by the facility from 1994–2003 (n = 1203 measurements) was grouped into two time periods (1994–99 and 2000–03), and three work categories (production, production support, and administration). For the period 1994–99, median beryllium levels were 0.20 μg/m^3, 0.10 μg/m^3, and

less than the limit of detection in production, production support and administration, respectively (n = 412, full-shift personal lapel samples). For the later period, median beryllium levels were 0.18 μg/m^3, 0.04 μg/m^3, and 0.02 μg/m^3 in production, production support, and administration, respectively (n = 791, full-shift personal lapel samples).

(c) Machining and use

Martyny *et al.* (2000) conducted particle-size selective sampling on five mechanical processes (milling, deburring, lapping, lathe operations, and grinding) to examine the particle size distribution of beryllium machining exposures. Two sets of stationary samples were collected using Lovelace Multijet Cascade Impactors mounted to the machines at 'point of operation' and at 'nearest worker location', two sets of personal samples were collected in the breathing zone of workers operating the machines (one personal pump-powered lapel sampler, one personal cascade impactor), as well as ambient air samples from four fixed locations in the facility. In total, 336 measurements were collected (79 personal pump samples, 87 personal impactor samples, 71 nearest worker location samples, 87 point of operation samples, and 12 ambient air samples. Of these, 243 were samples of the five target processes (64 personal pump samples, 59 personal impactor samples, 64 nearest worker location samples, and 56 point of operation samples). For the stationary area samples, median TWA concentrations were in the range of 0.20 μg/m^3 for the 'nearest worker location' samples to 0.60 μg/m^3 for the 'point of operation' samples. For the personal breathing zone samples (collected by the personal impactors), median TWA concentrations were in the range of 0.13 μg/m^3 for lapping processes to 0.74 μg/m^3 for deburring operations. The range of 48-hour median ambient concentration was 0.02–0.07 μg/m^3.

To evaluate the effectiveness of a beryllium exposure control programme at an atomic weapons facility in Wales, United Kingdom, Johnson *et al.* (2001) analysed 585438 air monitoring records (367757 area samples collected at 101 locations, and 217681 personal lapel samples collected from 194 workers during 1981–97). Across all departments, the range of annual personal concentrations was 0.11–0.72 μg/m^3 (mean) and 0.08–0.28 μg/m^3 (median). The highest levels of exposure were observed in foundry workers, with a mean exposure level of 0.87 μg/m^3 and a median exposure level of 0.22 μg/m^3 (over all years). For the area samples, mean annual concentrations ranged from a high of 0.32 μg/m^3 in 1985 to a low of 0.02 μg/m^3 in 1997.

(d) Alloy facilities

Schuler *et al.* (2005) analysed airborne beryllium measurements collected in 1969–2000 at a beryllium–copper alloy strip and wire finishing facility. Of the 5989 available measurements, 650 were personal samples, 4524 were general area samples, and 815 were short-duration, high-volume (SD-HV) breathing zone samples. Data were grouped and analysed on the basis of work category (production, production support, administration), and by process or job within each work category. For example, 'rod and wire' production is a subcategory of 'production'; jobs within 'rod and wire' production include: wire annealing and pickling, wire drawing, straightening, point and chamfer, rod and wire packing, die grinding, and, historically, wire rolling. Median plant-wide exposure levels were 0.02 μg/m^3 (personal), 0.09 μg/m^3 (general area), and 0.44 μg/m^3 (SD-HV breathing zone). Among work categories, the highest levels of beryllium exposure were found in 'rod and wire' production (median, 0.06 μg/m^3), with the most highly exposed process or job being 'wire annealing and pickling' (median, 0.12 μg/m^3).

In a study in a beryllium alloy facility, Day *et al.* (2007) measured levels of beryllium in workplace air (n = 10), on work surfaces (n = 252), on cotton gloves worn over nitrile gloves (n = 113),

and on necks and faces of workers (n = 109). In production, geometric mean levels of beryllium were 0.95 µg/100 cm^2 (work surfaces), 42.8 µg per sample (cotton gloves), 0.07 µg per sample (necks), and 0.07 µg per sample (faces). In production support, geometric mean levels of beryllium were 0.59 µg/100 cm^2 (work surfaces), 73.8 µg per sample (cotton gloves), 0.09 µg per sample (necks), and 0.12 µg per sample (faces). The lowest levels were measured in the administration section, with geometric mean levels of beryllium of 0.05 µg/100 cm^2 (work surfaces), 0.07 µg per sample (cotton gloves), 0.003 µg per sample (necks), and 0.003 µg per sample (faces). Strong correlations were observed between beryllium in air and on work surfaces (r = 0.79), and between beryllium on cotton gloves and on work surfaces (r = 0.86), necks (r = 0.87), and faces (r = 0.86).

Yoshida *et al.* (1997) studied airborne beryllium levels at two beryllium–copper alloy manufacturing factories in Japan during 1992–95. General area samples were collected in the beryllium–copper alloy process (n = 56) and the beryllium–copper metal mould manufacturing process (n = 41) of Factory A, and in the beryllium–copper cold rolling, drawing and heat-treatment process (n = 16) and beryllium–copper slitting treatment process (n = 8) of Factory B. In all years studied, the highest geometric mean beryllium levels were observed in the beryllium–copper alloy process of Factory A (range, 0.16–0.26 µg/m^3).

Stanton *et al.* (2006) studied beryllium exposures among workers at three beryllium–copper alloy distribution centres in the USA in 2000–01. For the period 1996–2004, company records of full-shift personal lapel breathing zone samples for airborne beryllium (n = 393) were examined. A total of 54% of all samples were at or below the limit of detection. The overall median beryllium concentration was 0.03 µg/m^3 (arithmetic mean, 0.05 µg/m^3). When examined by work category (production – bulk products, production – strip metal, production support, administration) and process or job within work category, concentration ranges were 0.01–0.07 µg/m^3 (median), and 0.02–0.07 µg/m^3 (geometric mean). The highest concentrations were measured in heat-treating (bulk products) and tensioning (strip metal) processes, with levels of 1.6 µg/m^3 and 1.4 µg/m^3, respectively.

(e) *Nuclear facilities*

Stange *et al.* (1996a) studied beryllium exposures in the Rocky Flats Nuclear Facility in the USA. Fixed airhead (i.e. area) samples (n = 102) and personal breathing zone samples (n = 102) were collected from the main beryllium production building. The mean beryllium concentration from the area samples was 0.16 µg/m^3, and from the personal samples, 1.04 µg/m^3. No correlation (r^2 = 0.029) was observed between fixed airhead and personal breathing zone beryllium samples.

Stefaniak *et al.* (2003a) investigated historical beryllium exposure conditions at the Los Alamos Nuclear Laboratory in the USA. A total of 4528 personal breathing zone and area samples were analysed. For all technical areas, the geometric mean concentration for the period 1949–89 was 0.04 µg/m^3. Average beryllium concentrations per decade were less than 1 µg/m^3, and annual geometric mean concentrations in the area that was the largest user of beryllium were generally below 0.1 µg/m^3.

(f) *Other*

Meeker *et al.* (2006) compared occupational exposures among painters using three alternative blasting abrasives (specular hematite, coal slag, steel grit) on a footbridge painting project during 2002–04 in New Jersey, USA. Over the 3-year project, personal breathing zone samples were collected outside the respirators of two or three abrasive blasters. The range of beryllium concentrations measured outside personal protective equipment (n = 18 samples) was 2.5–9.5 µg/m^3, with a geometric mean exposure

level of 5.0 μg/m^3. Beryllium was also measured in bulk paint chips collected from each bridge.

Bauxite, from which aluminium is derived, may contain beryllium in varying degrees. In 965 personal samples collected during 2000–05 in four aluminium smelters, beryllium concentrations varied in the range of 0.002–13.0 μg/m^3 (arithmetic and geometric means were 0.22 and 0.05 μg/m^3, respectively) (Taiwo *et al.*, 2008).

1.5.3 Dietary exposure

There is a lack of reliable data on the concentration of beryllium in food (WHO, 1990; ATSDR, 2002). Measured concentrations of beryllium have been reported for 38 foods, fruit and fruit juices from around the world (number of samples, 2243; 2209 foods + 34 fruit and juices). Concentrations in the foods have been reported in the range of < 0.1–2200 μg/kg fresh weight, with the highest concentrations measured in kidney beans, crisp bread, garden peas, parsley and pears (2200, 112, 109, 77, and 65 μg/kg fresh weight, respectively), and with a median concentration of 22.5 μg/kg fresh weight (kidney beans were excluded from this calculation). Concentrations in the fruits and juices ranged from not detected to 74.9 μg/L, with an average concentration of 13.0 μg/L (ATSDR, 2002). Beryllium has also been measured in rice, head lettuce, and potatoes at 80 μg/kg, 330 μg/kg, and 0.3 μg/kg, respectively (Kolanz, 2001).

1.5.4 Biomarkers of exposure

Several analytical methods are available and have adequate sensitivity for measuring beryllium in biological samples. These include gas chromatography-electron capture (GC-ECD), graphite furnace atomic absorption spectrometry (GF-AAS), inductively coupled plasma atomic emission spectrometry (ICP-AES), and inductively coupled plasma mass spectrometry (ICP-MS). Biological matrices in which these methods can measure beryllium include: blood, urine, faeces, fingernails, hair, and lung tissue. Urinary beryllium is an indicator of current exposure, but is of uncertain utility for quantitative exposure assessment. Beryllium levels in blood, serum or plasma are indicators of the intensity of current exposure (ATSDR, 2002; NTP, 2004; NRC 2007).

The average burden of beryllium in the general population is 0.20 mg/kg in the lung and is below 0.08 mg/kg in other organs (Kolanz, 2001).

The mean concentration of beryllium in urine measured in about 500 non-occupationally exposed individuals in the USA during the Third National Health and Nutrition Examination Survey (NHANES III) was 0.22 μg/g of creatinine (Paschal *et al.*, 1998). Other studies reported mean urinary beryllium concentrations in the range of < 0.03–0.4 μg/L for non-occupationally exposed individuals (Apostoli & Schaller, 2001).

2. Cancer in Humans

The previous *IARC Monograph* on beryllium and beryllium compounds was based largely on evidence of elevated lung cancer mortality among 689 individuals (predominantly workers) entered into the US Beryllium Case Registry (Steenland & Ward, 1991; Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-02-Table2.1.pdf), and in a cohort of 9225 workers employed at seven beryllium-processing plants in the USA (Ward *et al.*, 1992). The cohort study included two plants that had been previously studied (Mancuso, 1979, 1980; Wagoner *et al.*, 1980) and Infante *et al.* (1980) had reported earlier on mortality in the Beryllium Case Registry cohort.

2.1 Cohort studies and nested case–control studies

The body of evidence available for the current evaluation of the carcinogenicity of beryllium in humans includes the two previously evaluated cohort studies and a nested case–control study initially reported by Sanderson *et al.* (2001b), and reanalysed with adjustment for temporal confounders by Schubauer-Berigan *et al.* (2008).

The Beryllium Case Registry study included 689 individuals entered alive into the registry and followed for mortality through to 1988 (Steenland & Ward, 1991); 34% were from the fluorescent tube industry, and 36% were from basic manufacturing. There were 158 deaths from pneumoconiosis and other respiratory disease, the category that included beryllium disease (Standard Mortality Ratio [SMR], 34.2; 95%CI: 29.1–40.0). The overall SMR for lung cancer was 2.00 (95%CI: 1.33–2.89), based on 28 deaths. Among those with acute beryllium disease, there were 17 lung cancer deaths (SMR 2.32; 95%CI: 1.35–3.72), and among those with chronic beryllium disease, ten lung cancer deaths (SMR 1.57; 95%CI: 0.75–2.89).

The cohort study included workers at seven beryllium-processing plants in the USA involved in various phases of beryllium processing with exposure to many forms of beryllium and beryllium compounds (Ward *et al.*, 1992). The study found a significantly elevated SMR of 1.26 (95%CI: 1.12–1.42) for lung cancer in the cohort overall, with significant excesses observed for the two oldest plants located in Lorain, Ohio, and Reading, Pennsylvania.

The SMR for lung cancer at the Lorain plant was 1.69 (95%CI: 1.28–2.19), and at the Reading plant, 1.24 (95%CI: 1.03–1.48). The Lorain plant, in operation during 1935–48, is thought to have had very high beryllium exposures. The majority of workers (84.6%) were employed for less than 1 year. Ninety-eight of the 1192 individuals employed at the Lorain plant (8.2%) were identified in the Beryllium Case Registry as having beryllium disease; 91 were of the acute form which has only been associated with very high beryllium exposure, six individuals had chronic beryllium disease, and one was of unknown type. A total of 11 lung cancer deaths occurred among the 98 individuals with beryllium disease (SMR, 3.33; 95%CI: 1.66–5.95), and 46 lung cancer deaths occurred among the remaining 1094 Lorain workers (SMR, 1.51; 95%CI: 1.11–2.02). All but one of the 57 lung cancer deaths occurred in latency categories < 15 years; for 15–30 years' latency, the SMR was 2.09 [95%CI: 1.30–3.21]; and for over 30 years' latency, 1.66 [95%CI: 1.16–2.31].

The plant in Reading, Pennsylvania, in operation during 1935–2001, employed 3569 workers during 1940–69. Among those, 53.8% were employed for less than 1 year, and only 17.2% were employed for more than 10 years. When the SMRs for lung cancer at the Reading plant were analysed by latency and duration of exposure, the highest SMR was observed for the category with less than 1 year of employment and duration and more than 30 years' latency (SMR = 1.42; [95%CI: 1.01–1.93]). Further analyses by decade of hire revealed that 92/120 lung cancer deaths occurred among workers hired before 1950 (SMR, 1.26; [95%CI: 1.02–1.55]). None of the newer plants included in the study had a significantly elevated SMR for lung cancer. However, non-significantly elevated SMRs were observed for four out of five plants operating in the 1950s for workers hired during that decade. The results were adjusted for smoking based on comparing smoking histories of 1466 (15.9%) of cohort members surveyed in 1968 with a survey of the US population conducted in 1965, resulting in SMRs of 1.12, 1.49 and 1.09 for the total cohort, the Lorain plant, and the Reading plant, respectively. [The Working Group noted that it is unclear that adjustment for differences in smoking patterns between cohort members and the US population in the late 1960s would accurately reflect patterns

in the 1940s that would be most relevant to interpreting the lung cancer excess. It is possible that using data from the 1960s would overestimate the impact of smoking.] SMRs based on county referent rates were also presented and for the cohort as a whole, the SMR was slightly increased to 1.32, the SMR declined for the Lorain plant to 1.60, and increased for the Reading plant to 1.42.

Subsequent to the publication of the Ward *et al.* (1992) study, the Beryllium Industry Scientific Advisory Committee suggested that the excess of lung cancer observed at the Lorain plant might be attributable to exposure to sulfuric acid mist and fumes rather than exposure to beryllium (BISAC, 1997). A reanalysis of the cohort study used alternative referent rates (for cities in which the two oldest plants were located) to compute expected number of lung cancers, alternative smoking risk factor estimates to adjust for differences in smoking habits between the cohort and the US population, and an alternative methodology to calculate the SMR for all plants combined (Levy *et al.*, 2002). The net effect of the reanalysis was to reduce the magnitude and statistical significance of the SMRs in the Ward *et al.* (1992) study. [The Working Group noted that there are several potential methodological limitations of this reanalysis. For instance, the city referent rates used for the calculation were not published, whereas Ward *et al.* (1992) used only published rates.]

Sanderson *et al.* (2001b) conducted a nested case–control study of lung cancer within one of the beryllium processing plants studied by Ward *et al.* (1992). This plant was selected for study because it was one of the two older plants in which an elevated lung cancer SMR was observed, and because industrial hygiene measurement data were available from as early as 1947. Details of the job–exposure matrix are provided in Sanderson *et al.* (2001a). Mortality was followed-up through 1992, and 142 lung cancer cases were identified. Cases were age- and race-matched to five controls through incidence-density sampling (Sanderson *et al.*, 2001b). The main findings of the Sanderson *et al.* (2001b) study were positive associations with average and maximum exposure lagged 10 and 20 years. This association did not appear to be confounded by smoking in an analysis that excluded professional workers.

Following some letters and critiques of the Sanderson *et al.* (2001b) study (Deubner *et al.*, 2001b, 2007; Sanderson *et al.*, 2001c; Levy *et al.*, 2007), a reanalysis of the study was carried out that adjusted for year of birth and an alternative minimal exposure value (the lowest detectable exposure level divided by two) in continuous exposure–response analyses (Schubauer-Berigan *et al.*, 2008; see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-02-Table2.2.pdf). After controlling for year of birth, significantly elevated odds ratios for 10-year lagged average beryllium exposure were found in the middle two exposure quartiles. The choice of an alternative minimal exposure value decreased the trend statistic for cumulative exposure but increased it for average exposure. In the continuous analysis of average 10-year lag dose, the parameter estimates and *P*-values were highly significant with control for year of birth. [The Working Group noted that several methodological articles were published regarding the incidence-density sampling methods used in the nested case–control study (Deubner & Roth, 2009; Hein *et al.*, 2009; Langholz & Richardson, 2009; Wacholder, 2009). Three of these articles affirmed the methodology used to select controls in the study (Hein *et al.*, 2009; Langholz & Richardson, 2009; Wacholder, 2009). The Working Group noted that the issues raised in the Deubner & Roth (2009) commentary did not undermine confidence in the results of the Schubauer-Berigan *et al.* (2008) reanalysis.]

2.2 Synthesis

A large body of evidence was evaluated by the Working Group and, in conclusion, elevated lung cancer mortality was observed in a study of individuals with beryllium disease and in a cohort study of workers at seven beryllium-processing plants. The association of the elevated lung cancer risks with beryllium exposure is supported by a large number of lung cancer cases and stable rate ratios, a consistency in findings among plants, higher risks of lung cancer among workers hired before 1950 (when exposures were at their highest), a greater risk of lung cancer in the US Beryllium Case Registry cohort (especially among those highly exposed who were diagnosed with acute pneumonitis), and greatest risks for lung cancer in the plants with the highest risk for acute pneumonitis and other respiratory disease. In addition, the nested case–control studies found evidence for an exposure–response relationship that was strongest when using the 10-year lag average-exposure metric. All of the epidemiological studies involved potential exposure to metallic beryllium as well as other beryllium compounds, and were unable to discern the specific effects of beryllium metal or specific beryllium compounds.

3. Cancer in Experimental Animals

Beryllium compounds have been tested for carcinogenicity by inhalation in rats and mice, by intratracheal or intrabronchial administration in rats, by intravenous administration to rabbits, by intraperitoneally administration to mice, and by intramedullary bone administration in rabbits.

To date, by all routes of exposure and in all species tested, all beryllium compounds examined have been shown to be carcinogenic (IARC, 1993).

3.1 Inhalation exposure

3.1.1 Mouse

In p53 heterozygous mice, lung tumours occurred after a single series of three consecutive daily inhalation exposures to beryllium metal (Finch *et al.*, 1998a).

3.1.2 Rat

The first inhalation study published on beryllium was with beryllium sulfate in rats, which induced lung tumours and chronic lung disease (Schepers *et al.*, 1957). Inhalation of single doses of beryllium metal (Nickell-Brady *et al.*, 1994), and exposure to beryllium sulfate for 6 months (Schepers *et al.*, 1957) or 72 weeks (Reeves *et al.*, 1967) caused lung tumours in rats. Beryl ore dust induced lung tumours in rats (Wagner *et al.*, 1969).

3.1.3 Hamster

A study of inhalation of beryl ore for 17 months in hamsters resulted in excess atypical lung proliferative lesions, some of which described as tumours (Wagner *et al.*, 1969). It is noteworthy that similar doses caused tumours in rats (Wagner *et al.*, 1969).

See Table 3.1.

3.2 Intratracheal administration

3.2.1 Rat

A single intratracheal administration of beryllium metal, beryllium oxide, and beryllium hydroxide once per week for 15 weeks caused lung tumours in rats (Groth *et al.*, 1980). Beryllium oxide caused lung tumours in rats (Ishinishi *et al.*, 1980; Litvinov *et al.*, 1983).

See Table 3.2.

Table 3.1 Studies of cancer in experimental animals exposed to beryllium (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, p53 Heterozygous (M, F) 6–19 mo Finch *et al.* (1998a)	Beryllium metal Single exposure to 47 µg or 3×/d 63 µg 15/group/sex	Lung (tumours, both sexes combined): P53–controls 0/30, low dose 0/29, high dose 4/28 (14%) Wild-type–0/28	$P = 0.048$	
Rat, Wistar and Sherman (M, F) 18 mo (22 mo for controls) Schepers *et al.* (1957)	Beryllium sulfate tetrahydrate Inhalation 35.8 µg/m^3 5.5 d/wk during 180 d 84, 139 controls	Lung (tumours): 76 in 52 rats that survived after exposure period Controls–0/139	NR	Incomplete reporting of the study, total tumours not incidence reported, disease outbreak killed 58 rats during exposure and afterwards, data not divided up by strain or sex
Rat, SD CD rats (M, F) 72 wk Reeves *et al.* (1967)	Beryllium sulfate tetrahydrate Inhalation 34.25 µg/m^3 7 h/d, 5 d/wk, 150/group	Lung (pulmonary alveolar adenocarcinomas, multiple): 43/43 (100%) rats alive past 13 mo Controls–none	NR	Age at start, 6 wk Incomplete reporting of the study, respiratory infections, dead rats thrown out due to postmortem changes
Rat, Charles River CD (M) For each ore – up to 23 mo Wagner *et al.* (1969)	Beryl ore or bertrandite ore Inhalation 15mg/m^3, 6 h/d, 5 d/wk (210–620 µg/m^3 beryllium) 93, 33 controls	*Beryl* Lung: **12 mo** 5/11 (45%) squamous metaplasias or small epidermoid tumours **17 mo** 18/19 (95%) lung tumours (alveolar cell tumours–7 adenomas, 9 adenocarcinomas, 4 epidermoid tumours) *Bertrandite* None Controls, none	NR	High crystalline silica content of bertrandite ore Incomplete reporting of the study

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Hamster, Syrian golden (M) 17 mo Wagner *et al.* (1969)	Beryl ore or bertrandite ore Inhalation 15 mg/m^3, 6 h/d, 5 d/wk 48/group	*Both ores* **12 mo** Atypical lung proliferations **17 mo** More atypical lesions in beryl-exposed hamsters No definitive tumours	NR	Incomplete reporting of the study, lung lesions called adenomas in the figure only, but were probably adenomatous hyperplasias, and not tumours
Rats, F344 (M, F) 14 mo Nickell-Brady *et al.* (1994)	Beryllium metal Inhalation (nose-only) Single exposure 40, 110, 360 and 430 µg (cohort of Lovelace High dose study) 30/group/sex	Lung (tumours): 64% Controls, NR		Age at start, 12 wk No incidence data by group or sex

d, day or days; F, female; h, hour or hours; M, male; mo, month or months; NR, not reported; wk, week or weeks

Table 3.2 Studies of cancer in experimental animals exposed to beryllium (intratracheal or intrabronchial exposure)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar (F) 18 mo Groth *et al.* (1980)	Intratracheal single exposure to 0.5 or 2.5 mg beryllium metal or beryllium–aluminum alloy, beryllium–copper alloy, beryllium–copper–cobalt alloy, beryllium–nickel alloy 35/group	Lung (adenomas or carcinomas): Beryllium metal– 2/3 (67%) low dose, 6/6 (100%) high dose Passivated beryllium metal– 7/11 (64%) low dose, 4/4 (100%) high dose Alloy groups– all negative Controls, 0/21 after 19 mo Beryllium hydroxide– 13/25 (52%) adenoma or adenocarcinoma	$P < 0.008$	Age at start, 3 mo Low beryllium content of alloys Incidence of animals sacrificed at 19 mo reported
Rat, Wistar (F) 19 mo Groth *et al.* (1980)	Intratracheal 50 µg beryllium hydroxide initially followed by 25 µg 10 mo later 35/group	Lung (tumours): 13/25 (52%); Controls, 0/21	$P = 0.0021$	Incidence in rats surviving 16 mo or more
Rat, Wistar (M) Life span Ishinishi *et al.* (1980)	Intratracheal instillation 1 mg beryllium oxide once/wk for 15 wk 30; 16 controls	Lung (tumours): 6/30 (20%, 4 benign, 2 malignant) Controls, 0/16		Animals/group at start NR Untreated controls, 3/4 adenomas have histology indicative of malignancy
Rat, albino (NR) Life span Litvinov *et al.* (1983)	Intratracheal Single exposure beryllium oxide, low- and high-temp fired 0.036, 0.36, 3.6, 18 mg/kg 300 controls	Lung (tumours, malignant): High temp fired– 0/76, 0/84, 2/77 (3%), 2/103 (2%) Low temp fired– 3/69 (4%), 7/81 (9%), 18/79 (23%), 8/26 (31%) Controls, 0/104	NR	

d, day or days; F, female; h, hour or hours; M, male; mo, month or months; NR, not reported; wk, week or weeks

Table 3.3 Studies of cancer in experimental animals exposed to beryllium (intravenous exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse Strain, sex and duration, NR Cloudman *et al.* (1949)	Zinc beryllium silicate (0.264 mg Be); beryllium oxide (1.54 mg Be) 20–22 injections (twice weekly) Number at start, NR	"Some mice" developed malignant bone tumours		Animals/group at start NR Only zinc beryllium silicate induced osteosarcomas
Rabbit Strain, sex and duration, NR Barnes & Denz (1950)	Beryllium metal Total dose, 40mg 24 animals	Bone (sarcomas): 2 surviving rabbits		Toxicity in 19 rabbits during first wk and mo (liver necrosis)
Rabbit Strain and sex, NR > 7 mo Gardner & Heslington (1946)	Zinc beryllium silicate and beryllium oxide 20 doses, total dose–1 g of particles 7 animals	Osteosarcomas: *Zinc beryllium silicate*– 7/7 (100%) that lived past 7 mo *Beryllium oxide*– 1		
Rabbit Strain and sex, NR > 1 yr Cloudman *et al.* (1949)	Zinc beryllium silicate (17 mg Be) or beryllium oxide (390 mg Be) 20–22 injections (twice weekly)	Bone (tumours): *Zinc beryllium silicate*– 4/5 (80%)		Animals/group at start NR
Rabbit Strain, NR (M, F) > 30 wk Barnes & Denz (1950)	Zinc beryllium silicate or beryllium silicate 6–10 injections 67 animals	Bone (sarcomas): *Zinc beryllium silicate*– 7/21 (33%) past 30 wk		Poor survival
Rabbit Strain, NR (M, F) > 11.5 mo Dutra & Largent (1950)	Beryllium oxide or calcined phosphor with beryllium oxide, zinc oxide and silica 20–26 injections 360–700 mg beryllium in beryllium oxide 64–90 mg beryllium in phosphor group	Osteosarcomas: *Beryllium oxide*– 6/6 (100%) *Phosphor*– 2/3 (67%) Controls, 0/50		Animals/group at start NR
Rabbit Strain, NR (M, F) 14–28 mo Hoegland *et al.* (1950)	Beryllium phosphate Zinc beryllium silicate Beryllium oxide 1–4-d intervals, unknown time period Doses not clear 24 animals	Osteosarcomas: *Zinc beryllium silicate*– 7/8 (88%) *Beryllium oxide*– 1		Small group size, lack of controls Incomplete reporting

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rabbit Strain and sex, NR 18 mo Araki *et al.* (1954)	Beryllium phosphate 1 g Beryllium oxide 1 g Beryllium oxide + zinc oxide Single dose 35 animals	Osteosarcomas: *Beryllium phosphate–* 2/4 (50%) *Beryllium oxide+zinc oxide–* 9/31 (29%)		Weight ≈2.0 kg Small numbers of animals, no appropriate controls
Rabbit (M) Strain, NR Jaques *et al.* (1954)	Zinc beryllium silicate (1 g beryllium silicate, 33.6 mg beryllium oxide) Twice/wk for 10 wk 10 animals	Osteosarcomas: 5		Age at start, 9–11 mo Small group size, lack of controls
Rabbit Strain and sex, NR 57 wk Kelly *et al.* (1961)	Zinc beryllium silicate Twice/wk for 10 wk 14 animals	Osteosarcomas: 10/14 (71%)		Small group size, lack of controls
Rabbit Strain and sex, NR 15–18 mo Konikowski (1967)	Beryllium oxide Single 1 g dose 20 animals	Osteosarcomas: 3/20 (15%)		Lack of appropriate control group
Rabbit Strain and sex, NR 25 wk Endo (1972)	Beryllium oxide (1%) Once/wk for 25 wk 60 animals	Sarcomas: 21/29 (72%)		Age at start, 6 mo Incomplete reporting, lack of appropriate control group

d, day or days; F, female; M, male; mo, month or months; NR, not reported; wk, week or weeks

Table 3.4 Studies of cancer in experimental animals exposed to beryllium (other routes of exposure)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, A/J (M) 32 wk Ashby *et al.* (1990)	Intraperitoneal Beryllium sulfate tetrahydrate 0, 0.02, 0.05, 0.1 mg/mouse/injection 3×/wk for 8 wk 20/group	Incidence (% given only): 15, 17, 33, 38% Lung tumours/mouse: 0.15, 0.17, 0.39, 0.38	r = 5.9 and 4.6 for middle and high doses (χ^2)	Age at start, 5–6 wk Purity, 99% Middle and high doses, significant
Rabbit Strain and sex, NR 1–2 yr Yamaguchi (1963)	Injection into bone marrow Beryllium oxide 10 mg twice/wk 55 animals	Bone (tumours): 26		
Rabbit, mixed breeds (M, F) 15–20 mo Tapp (1960)	Intramedullary injection Beryllium silicate powder 20 mg 12 animals	Osteogenic sarcomas: 4/12 (33%)		Age at start, 6 wk
Rabbit, mixed breeds (M, F) 25 mo Tapp (1969)	Implants (periosteal) Zinc beryllium silicate, beryllium oxide, beryllium silicate 10 mg 18 animals	Osteogenic sarcomas: 4/18 (22%)		Age at start, 6 and 8 wk
Rabbit Strain and sex, NR 24 mo Komitowski (1974)	Intramedullary injection Beryllium oxide No dose given 20 animals	Osteogenic sarcomas: 5/20 (25%)		Incomplete reporting, lack of appropriate control group
Rabbit Strain and sex, NR 21 mo Matsuura (1974)	Intramedullary implants Beryllium carbonate, beryllium acetate, beryllium acetylacetonate, beryllium laurate, beryllium stearate 173, 18, 3, 3	Osteosarcomas: *Beryllium carbonate*– 30 *Beryllium acetylacetonate*– 1		Incomplete reporting, small numbers in most groups
Rabbit, Fauve de Bourgogne, sex (NR) > 4 mo Mazabraud (1975)	Intraosseous injection Zinc beryllium silicate 1 g/cm^3 65 animals	Osteogenic sarcomas: 45/65 (69%)		Age at start, 15–20 wk Incomplete reporting Lack of appropriate control group
Rabbit (M) 56 wk Hiruma (1991)	Implants into bone Beryllium oxide 300 (after fracture), 300, 50 mg 10/group	Osteosarcomas: 10/10 (100%) 7/10 (70%) 1/10 (10%)		

F, female; M, male; mo, month or months; NR, not reported; wk, week or weeks; yr, year or years

3.3 Intravenous administration

3.3.1 Mouse

A mouse study reported bone tumours after intravenous injection of zinc beryllium silicate (Cloudman *et al.*, 1949).

3.3.2 Rabbit

Multiple intravenous injections of beryllium metal (Barnes & Denz, 1950), beryllium oxide (Gardner & Heslington, 1946; Dutra & Largent, 1950; Araki *et al.*, 1954; Komitowski, 1967; Fodor, 1977), beryllium silicate, beryllium phosphate (Araki *et al.*, 1954), and zinc beryllium silicate (Gardner & Heslington, 1946; Cloudman *et al.*, 1949; Barnes & Denz, 1950; Hoagland *et al.*, 1950; Janes *et al.*, 1954; Kelly *et al.*, 1961) caused osteosarcomas in rabbits, which were reviewed by Groth (1980).

See Table 3.3.

[The Working Group noted that although many of these studies had defficiency in reporting methods, the rarity of the induced tumours was considered to be compelling enough to consider them as a group.]

3.4 Other routes of exposure

3.4.1 Mouse

Beryllium sulfate injected intraperitoneally caused an increased incidence and multiplicity of lung tumours in A/J mice (Ashby *et al.*, 1990).

3.4.2 Rabbit

Intramedullary bone administration of beryllium oxide (Yamaguchi, 1963; Komitowski, 1974; Hiruma, 1991), beryllium silicate (Tapp, 1966), zinc beryllium silicate (Tapp, 1969; Mazabraud, 1975), beryllium carbonate (Matsuura, 1974), and beryllium acetylacetonate (Matsuura, 1974) caused osteosarcomas or other bone tumours in rabbits.

See Table 3.4.

3.5 Synthesis

Lung tumours were induced in rats by inhalation of beryllium sulfate, beryllium metal, and beryl ore dust. In mice, lung cancer occurred after inhalation of beryllium metal. In hamsters, inhalation of beryl ore induced adenomatous hyperplasia of the lung. Intratracheal instillation of beryllium metal, beryllium hydroxide, and beryllium oxide in rats induced lung tumours. Intraperitoneal injection of beryllium sulfate induced lung tumours in mice. Intravenous injection or intramedullary injection/implantation of various beryllium compounds induced osteosarcoma in various studies in rabbits, and in one study in mice.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

The bioavailability of beryllium particles as a function of size (geometric mean diameter), chemical composition, and specific surface area has been studied extensively. The agglomeration of beryllium particles does occur but the agglomerates dissociate again in fluid, with a corresponding decrease in particle mean diameter (Kent *et al.*, 2001; Stefaniak *et al.*, 2003b, 2004, 2007). Highly significant associations of chronic beryllium disease (CBD) and beryllium sensitization with particle-mass concentration for particles of less than 10 μm have been observed. The particle-mass concentration of alveolar-deposited particles (< 10 μm) correlates significantly with the occurrence of CBD. In a simulated phagolysosomal fluid, dissolution rate constants (k) for metallic beryllium particles and multiconstituent particles from arc-furnace processing of a beryllium–copper alloy were greater than those observed for beryllium oxide materials (Stefaniak *et al.*, 2006). Beryllium has

been detected in CBD-associated granulomas of beryllium-exposed workers by secondary ion mass-spectroscopy at an average of 9 years post exposure (Sawyer *et al.*, 2005a). These data indicate that beryllium is retained in granulomatous lesions for extended periods of time in exposed humans with CBD. Verma *et al.*, (2003) also reported elevated concentrations of beryllium in lung tissue from a person with CBD.

Acute inhalation dose–response studies in mice with a follow-up period of 350 days showed that high-dose exposures produced granulomatous beryllium lesions, which impeded the clearance of beryllium from the lungs (Finch *et al.*, 1998b).

Accidental exposure of 25 people to beryllium dust produced a mean serum concentration of 3.5 μ/L measured one day later, which decreased to a mean concentration of 2.4 μ/L after 6 days (Zorn *et al.*, 1986). These data indicate that beryllium from beryllium metal is biologically available from the lung. Exposure to beryllium metal (Williams, 1977) and beryllium alloys (Lieben *et al.*, 1964) have been reported to produce beryllium disease.

4.2 Genetic and related effects

4.2.1 Direct genotoxicity

A large number of mutagenicity studies for beryllium compounds have been published (for reviews see IARC, 1993; Gordon & Bowser, 2003). In general, results of these studies have been either negative or weakly positive, depending on the test system used.

Joseph *et al.* (2001) studied gene expression patterns in BALB/c-3T3 cells transformed with beryllium sulfate and reported a general upregulation of several cancer-related genes. Because no toxicity data were provided in these studies, the relevance of these findings to cancer cannot be interpreted. The same authors also reported the downregulation of several genes involved in DNA synthesis, repair and recombination in the tumour cells relative to controls.

Fahmy *et al.* (2008) studied the genotoxicity of beryllium chloride in mice exposed to oral doses of 93.75–750 mg/kg body weight for 3 weeks. Starting with the second lowest concentration (187.5 mg/kg bw; 1/8 of the LD_{50}), chromosomal aberrations (excluding gaps) and aneuploidy were observed both in bone-marrow cells and in spermatocytes, as a function of dose and time.

4.2.2 Indirect effects related to genotoxicity

(a) Oxidative stress

Palmer *et al.* (2008) demonstrated upregulation of the protein PD-1 (programmed death-1) in beryllium-specific CD4+ T-cells derived from broncho-alveolar lavages from beryllium-sensitized persons or CBD patients. Upregulation of PD-1 was closely correlated with the severity of T-cell alveolitis.

Subsequent studies by Sawyer *et al.* (2005b) in mouse macrophages demonstrated beryllium-induced formation of reactive oxygen species *in vitro*, with marked increases in apoptosis and activation of caspase 8. These effects were attenuated by the addition of the antioxidant manganese(III)*meso*-tetrakis(4-benzoic acid) porphyrin (MnTBAP).

The inflammatory processes associated with the development of acute or chronic beryllium disease could plausibly contribute to the development of lung cancer by elevating the rate of cell turnover, by enhancing oxidative stress, and by altering several signalling pathways involved in cell replication.

(b) Epigenetic mechanisms

Studies by Belinsky *et al.* (2002) in beryllium-induced rat lung tumours demonstrated hypermethylation of the *p16* and *estrogen-receptor-α* genes, and their attendant inactivation.

4.3 Synthesis

Several molecular mechanisms, possibly interrelated, operate in beryllium-induced carcinogenesis. Whereas mutagenicity tests with beryllium have shown only weakly positive or negative results, chromosomal aberrations and aneuploidy were observed *in vivo* in mice, at non-toxic concentrations. Like many other carcinogenic metals, beryllium is capable of producing oxidative stress, which can lead to cell injury in the form of DNA damage, activation of proto-oncogenes, and apoptotic mechanisms. In addition, the toxicity of beryllium in the lung may lead to cell killing and compensatory cell proliferation. Furthermore, the beryllium-induced chronic inflammatory response with attendant release of cytokines from beryllium-reactive CD4+ T-cells could also play a role in the development of a carcinogenic response in lung tissue.

In addition to beryllium-mediated generation of reactive oxygen species, inflammatory processes induced by beryllium may also cause an increase in reactive oxygen species, mediate cell turnover, and alter cell-signalling pathways. Furthermore, downregulation of genes involved in DNA synthesis, repair and recombination also occurs. Thus, the processes underlying beryllium-induced carcinogenesis are clearly complex, with several possible interactive mechanisms.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of beryllium and beryllium compounds. Beryllium and beryllium compounds cause cancer of the lung.

There is *sufficient evidence* in experimental animals for the carcinogenicity of beryllium and beryllium compounds.

Beryllium and beryllium compounds are *carcinogenic to humans (Group 1).*

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CADMIUM AND CADMIUM COMPOUNDS

Cadmium and cadmium compounds were considered by previous IARC Working Groups in 1972, 1975, 1987, and 1993 (IARC, 1973, 1976, 1987, 1993a). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms, trade names and molecular formulae for cadmium, cadmium–copper alloy, and some cadmium compounds are presented in Table 1.1. The cadmium compounds shown are those for which data on carcinogenicity or mutagenicity were available or which are commercially important compounds. It is not an exhaustive list, and does not necessarily include all of the most commercially important cadmium-containing substances.

1.2 Chemical and physical properties of the agents

Cadmium (atomic number, 48; relative atomic mass, 112.41) is a metal, which belongs to group IIB of the periodic table. The oxidation state of almost all cadmium compounds is +2, although a few compounds have been reported in which it is +1. Selected chemical and physical properties of cadmium compounds are presented in the previous *IARC Monograph* (IARC, 1993a).

1.3 Use of the agents

Cadmium metal has specific properties that make it suitable for a wide variety of industrial applications. These include: excellent corrosion resistance, low melting temperature, high ductility, high thermal and electrical conductivity (National Resources Canada, 2007). It is used and traded globally as a metal and as a component in six classes of products, where it imparts distinct performance advantages. According to the US Geological Survey, the principal uses of cadmium in 2007 were: nickel–cadmium (Ni–Cd) batteries, 83%; pigments, 8%; coatings and plating, 7%; stabilizers for plastics, 1.2%; and other (includes non-ferrous alloys, semiconductors and photovoltaic devices), 0.8% (USGS, 2008).

Cadmium is also present as an impurity in non-ferrous metals (zinc, lead, and copper), iron and steel, fossil fuels (coal, oil, gas, peat, and wood), cement, and phosphate fertilizers. In these products, the presence of cadmium generally does not affect performance; rather, it is regarded as an environmental concern (International Cadmium Association, 2011). Cadmium is also produced from recycled materials (such as Ni–Cd batteries and manufacturing scrap) and some

Table 1.1 Chemical names, synonyms (CAS names are in italics), and molecular formulae of cadmium and cadmium compounds

Chemical name	CAS Reg. No.[a]	Synonyms	Formula
Cadmium	7440-43-9	Cadmium metal	Cd
Cadmium acetate	543-90-8 (24 558-49-4; 29 398-76-3)	*Acetic acid, cadmium salt*; bis(acetoxy)-cadmium; cadmium (II) acetate; cadmium diacetate; cadmium ethanoate	$Cd(CH_3COO)_2$
Cadmium carbonate	513-78-0 [93820-02-1]	*Carbonic acid, cadmium salt*; cadmium carbonate ($CdCo_3$); cadmium monocarbonate	$CdCO_3$
Cadmium chloride	10 108-64-2	Cadmium dichloride; dichlorocadmium	$CdCl_2$
Cadmium hydroxide	21 041-95-2 (1 306-13-4; 13 589-17-8)	*Cadmium hydroxide ($Cd(OH)_2$)*; cadmium dihydroxide	$Cd(OH)_2$
Cadmium nitrate	10 325-94-7 (14 177-24-3)	*Nitric acid, cadmium salt*; cadmium dinitrate; cadmium (II) nitrate	$Cd(NO_3)_2$
Cadmium stearate	2223-93-0	Cadmium distearate; cadmium octadecanoate; cadmium(II) stearate; octadecanoic acid, cadmium salt; *stearic acid, cadmium salt*	$Cd(C_{36}H_{72}O_4)$
Cadmium sulfate	10 124-36-4 (62 642-07-3) [31119-53-6]	Cadmium monosulfate; cadmium sulfate; *sulfuric acid, cadmium salt (1:1)*	$CdSO_4$
Cadmium sulfide	1306-23-6 (106 496-20-2)	Cadmium monosulfide; cadmium orange; cadmium yellow	CdS
Cadmium oxide	1306-19-0	Cadmium monoxide	CdO
Cadmium–copper alloy[b]	37 364-06-0	*Copper base, Cu, Cd*	Cd.Cu
	12 685-29-9 (52 863-93-1)	*Cadmium nonbase, Cd, Cu*	
	132 295-56-8	*Copper alloy, base, Cu 99.75–100, Cd 0.05–0.15*; UNS C14300	
	132 295-57-9	*Copper alloy, base, Cu 99.60–100, Cd 0.1–0.3*; UNS C14310	

[a] Replaced CAS Registry numbers are shown in parentheses; alternative CAS Registry numbers are shown in brackets.
[b] Sample of cadmium–copper alloys registered with the Chemical Abstracts Service

residues (e.g. cadmium-containing dust from electric arc furnaces) or intermediate products. Recycling accounts for approximately 10–15% of the production of cadmium in developed countries (National Resources Canada, 2007).

The primary use of cadmium, in the form of cadmium hydroxide, is in electrodes for Ni–Cd batteries. Because of their performance characteristics (e.g. high cycle lives, excellent low- and high-temperature performance), Ni–Cd batteries are used extensively in the railroad and aircraft industry (for starting and emergency power), and in consumer products (e.g. cordless power tools, cellular telephones, camcorders, portable computers, portable household appliances and toys) (ATSDR, 2008; USGS, 2008).

Cadmium sulfide compounds (e.g. cadmium sulfide, cadmium sulfoselenide, and cadmium lithopone) are used as pigments in a wide variety of applications, including engineering plastics, glass, glazes, ceramics, rubber, enamels, artists colours, and fireworks. Ranging in colour from yellow to deep-red maroon, cadmium pigments have good covering power, and are highly resistant to a wide range of atmospheric and environmental conditions (e.g. the presence of hydrogen

sulfide or sulfur dioxide, light, high temperature and pressure) (Herron, 2001; ATSDR, 2008; International Cadmium Association, 2011).

Cadmium and cadmium alloys are used as engineered or electroplated coatings on iron, steel, aluminium, and other non-ferrous metals. They are particularly suitable for industrial applications requiring a high degree of safety or durability (e.g. aerospace industry, industrial fasteners, electrical parts, automotive systems, military equipment, and marine/offshore installations) because they demonstrate good corrosion resistance in alkaline or salt solutions, have a low coefficient of friction and good conductive properties, and are readily solderable (UNEP, 2008; International Cadmium Association, 2011).

Cadmium salts of organic acids (generally cadmium laurate or cadmium stearate, used in combination with barium sulfate) were widely used in the past as heat and light stabilizers for flexible polyvinyl chloride and other plastics (Herron, 2001; UNEP; 2008). Small quantities of cadmium are used in various alloys to improve their thermal and electrical conductivity, to increase the mechanical properties of the base alloy (e.g. strength, drawability, extrudability, hardness, wear resistance, tensile, and fatigue strength), or to lower the melting point. The metals most commonly alloyed with cadmium include copper, zinc, lead, tin, silver and other precious metals. Other minor uses of cadmium include cadmium telluride and cadmium sulfide in solar cells, and other semiconducting cadmium compounds in a variety of electronic applications (Morrow, 2001; UNEP, 2008; International Cadmium Association, 2011).

Traditionally, the most common end-use applications for cadmium were pigments, stabilizers, and coatings. However, in recent years, the use of cadmium for these purposes has declined, mainly due to concerns over the toxicity of cadmium, and the introduction of regulations, particularly in the European Union, restricting its use (National Resources Canada, 2007).

1.4 Environmental occurrence

Historical information on the occurrence of cadmium and cadmium compounds can be found in the previous *IARC Monograph* (IARC, 1993a).

Cadmium occurs naturally in the earth's crust and in ocean water. It is emitted to the environment as a result of both natural and anthropogenic activities. Natural sources of cadmium include volcanic activity, weathering of cadmium-containing rocks, sea spray, and mobilization of cadmium previously deposited in soils, sediments, landfills, etc. Anthropogenic sources of cadmium include the mining and smelting of zinc-bearing ores, the combustion of fossil fuels, waste incineration, and releases from tailings piles or municipal landfills (UNEP, 2008; ATSDR, 2008).

1.4.1 Natural occurrence

In the earth's crust, cadmium appears mainly in association with ores containing zinc, lead, and copper (in the form of complex oxides, sulfides, and carbonates). Elemental cadmium is a soft, silver-white metal, which is recovered as a by-product of zinc mining and refining. The average terrestrial abundance of cadmium is 0.1–0.2 mg/kg, although higher concentrations are found in zinc, lead, and copper ore deposits. Naturally occurring cadmium levels in ocean water range, on average, from < 5 to 110 ng/L. (National Resources Canada, 2007; ATSDR, 2008; UNEP, 2008)

1.4.2 Air

Particulate cadmium (as elemental cadmium and cadmium oxide, sulfide or chloride) is emitted to the atmosphere from both natural and anthropogenic sources. Weathering and erosion of cadmium-bearing rocks is the most important natural source of cadmium. Other natural sources include volcanoes, sea spray, and

forest fires. The principal anthropogenic sources are non-ferrous metal production and fossil fuel combustion, followed by ferrous metal production, waste incineration, and cement production (WHO, 2000; ATSDR, 2008; UNEP, 2008)

Cadmium does not break down in the environment. Atmospheric cadmium compounds are transported (sometimes for long distances) and deposited (onto surface soils and water) with minimal transformation in the atmosphere (ATSDR, 2008). There is uncertainty about the relative magnitude of natural emissions versus anthropogenic emissions. Total global anthropogenic emissions in the mid-1990s were estimated at approximately 3000 tonnes. During 1990–2003, anthropogenic emissions of cadmium reportedly decreased by about half in Europe, and by about two-thirds in Canada (UNEP, 2008).

Mean total cadmium concentrations in air vary according to proximity to industrial source, and to population density. Measurement data from northern Europe for the period 1980–88 were reported as being around 0.1 ng/m^3 in remote areas, 0.1–0.5 ng/m^3 in rural areas, 1–10 ng/m^3 in urban areas, and 1–20 ng/m^3 in industrial areas, with levels of up to 100 ng/m^3 being observed near emission sources (WHO, 2000). Similar variations were observed in the USA (UNEP, 2008).

1.4.3 Water

Cadmium enters the aquatic environment from numerous diffuse (e.g. agricultural and urban run-off, atmospheric fall-out) and point sources, both natural and anthropogenic. Weathering and erosion of cadmium-containing rocks result in the release of cadmium not only to the atmosphere, but also to the soil and the aquatic system (directly and through the deposition of airborne particles) (ATSDR, 2008; UNEP, 2008). Cadmium is released to the aquatic environment from a range of anthropogenic sources, including non-ferrous metal mining and smelting (from mine drainage water, waste water, tailing pond overflow, rainwater run-off from mine areas), plating operations, phosphate fertilizers, sewage-treatment plants, landfills, and hazardous waste sites (IARC, 1993a; ATSDR, 2008).

Weathering and erosion are estimated to contribute 15000 tonnes of cadmium annually to the global aquatic environment, while atmospheric fall-out (of anthropogenic and natural emissions) is estimated to contribute between 900 and 3600 tonnes (UNEP, 2008).

1.4.4 Soil and sediments

Natural and anthropogenic sources (e.g. mine/smelter wastes, commercial fertilizers derived from phosphate ores or sewage sludge, municipal waste landfills) contribute to the levels of cadmium found in soil and sediments. Wet or dry deposition of atmospheric cadmium on plants and soil can lead to cadmium entering the food-chain through foliar absorption or root uptake. The rate of cadmium transfer depends on a variety of factors, including deposition rates, type of soil and plant, the pH of the soil, humus content, availability of organic matter, treatment of the soil with fertilizers, meteorology, and the presence of other elements, such as zinc (WHO, 2000; UNEP, 2008). Reported sediment concentrations of cadmium range from 0.03–1 mg/kg in marine sediments to as high as 5 mg/kg in river and lake sediments (Nordic Council of Ministers, 2003). Relatively high concentrations of cadmium (> 1 mg/kg) have been measured in the soil near smelters and other industrialized areas (WHO, 2000).

1.5 Human exposure

1.5.1 Exposure of the general population

The non-smoking general population is exposed to cadmium primarily via ingestion of food and, to a lesser extent, via inhalation of

ambient air, ingestion of drinking-water, contaminated soil or dust. For the US population, the geometric mean daily intake of cadmium in food is estimated to be 18.9 µg/day. In most countries, the average daily intake of cadmium in food is in the range of 0.1–0.4 µg/kg body weight (CDC, 2005; ATSDR, 2008; UNEP, 2008; EFSA, 2009)

Because tobacco leaves naturally accumulate large amounts of cadmium (Morrow, 2001), cigarettes are a significant source of cadmium exposure for the smoking general population. It has been estimated that tobacco smokers are exposed to 1.7 µg cadmium per cigarette, and about 10% is inhaled when smoked (Morrow, 2001; NTP, 2005). Data on blood and urine levels of smokers are found in Section 1.6.

1.5.2 Occupational exposure

The main route of cadmium exposure in the occupational setting is via the respiratory tract, although there may be incidental ingestion of dust from contaminated hands, and food (ATSDR, 2008). Occupations in which the highest potential exposures occur include cadmium production and refining, Ni–Cd battery manufacture, cadmium pigment manufacture and formulation, cadmium alloy production, mechanical plating, zinc smelting, brazing with a silver–cadmium–silver alloy solder, and polyvinylchloride compounding. Although levels vary widely among the different industries, occupational exposures generally have decreased since the 1970s. For more details on historical occupational exposures to cadmium, see the previous *IARC Monograph* (IARC, 1993a).

Estimates of the number of workers potentially exposed to cadmium and cadmium compounds have been developed by CAREX in Europe. Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX (CARcinogen EXposure) database estimates that 207350 workers were exposed to cadmium and cadmium compounds in the European Union, with over 50% of workers employed in the construction (n = 32113), manufacture of fabricated metal products (n = 23541), non-ferrous base metal industries (n = 22290), manufacture of plastic products not elsewhere classified (n = 16493), personal and household services (n = 15004), and manufacture of machinery except electrical (n = 13266).

CAREX Canada estimates that 35000 Canadians (80% males) are exposed to cadmium in their workplaces (CAREX Canada, 2011). The largest exposed group are workers in polyvinyl chloride plastic product manufacturing (n = 12000), who are exposed to cadmium-bearing stabilizers. Other industries in which exposure occurs include: foundries, commercial and industrial machinery manufacturing, motor vehicle parts manufacture, architectural and structural metal manufacturing, non-ferrous metal (except aluminium) production and processing, metalworking machinery manufacturing, iron and steel mills and ferro-alloy manufacturing, alumina and aluminium production and processing, and other electrical equipment and component manufacture.

Data from studies published since the previous *IARC Monograph* on exposure to cadmium and cadmium compounds in different occupational situations are summarized below.

(a) Battery manufacture

Zhang *et al.* (2002) investigated the renal damage of cadmium-exposed workers in an Ni–Cd battery factory in the People's Republic of China between April and May 1998. Based on area sampling measurements collected during 1986–92, the geometric mean concentration of cadmium oxide dust was 2.17 mg/m^3, with a range of 0.1–32.8 mg/m^3. The overall geometric mean urinary cadmium concentration for the 214 workers was 12.8 µg/g creatinine (range of geometric means, 4.0–21.4 µg/g creatinine), and the overall geometric mean blood cadmium

concentration was 9.5 µg/L (range of geometric means, 3.8–17.4 µg/L).

Cumulative exposure to cadmium hydroxide in Ni–Cd battery workers in the United Kingdom (n = 926 male workers) was investigated during 1947–2000. Mean cadmium concentrations in air from personal samples were highest in the 1969–73 period (range, 0.88–3.99 mg/m^3), and were lowest in the 1989–92 period (range, 0.024–0.12 mg/m^3). Mean cadmium concentrations in air from static area samples were highest in the 1954–63 period (range, 0.35–1.29 mg/m^3), and were lowest in the 1989–92 period (range, 0.002–0.03 mg/m^3) (Sorahan & Esmen, 2004).

(b) Cadmium recovery

Occupational exposure to cadmium compounds (oxide, sulfide, and sulfate) was investigated in male production workers (n = 571) from a cadmium recovery facility in the USA during 1940–82. Estimates of airborne cadmium exposures in the production departments ranged from 0.2 (in the tankhouse) to 1.5 mg/m^3 (in the mixing, calcine and retort departments) before 1950, and from 0.02 (in the tankhouse) to 0.6 mg/m^3 (in the sampling and roaster departments) for the 1965–76 time period (Sorahan & Lancashire, 1997).

(c) Cadmium alloy production

Occupational exposure to cadmium oxide fumes was investigated in 347 copper–cadmium alloy workers, 624 workers employed in the vicinity of copper–cadmium alloy work, and 521 iron and brass foundry workers in England and Wales during 1922–80. Based on a review of 933 measurements of airborne cadmium made during 1951–83 (697 area samples, 236 personal samples), cumulative cadmium exposures were estimated to be 600 µg/m^3 for the 1926–30 time period, dropping to an estimated 56 µg/m^3 by the 1980s (Sorahan *et al.*, 1995).

(d) Smelting

Occupational exposure to cadmium was investigated in 1462 male employees in a tin smelter in the United Kingdom during 1972–91. Annual average exposures in the principal process areas were reported. Average air levels were negligible in the dry-refining and electro-refining areas, low in the raw materials handling and roasters and ball mill areas (range of averages, 0.005–0.008 mg/m^3), and moderate in the sintering and blast furnace areas (range of averages, 0.04–0.08 mg/m^3) (Jones *et al.*, 2007).

(e) Vehicle manufacture

Wang *et al.* (2006) evaluated the exposure to metals of 82 welders and 51 operators in two vehicle-manufacturing plants in China. The geometric mean concentration of cadmium in the blood of welders was 3.54 µg/L (range, 0.2–12.5 µg/L), and was significantly higher than the control group concentration of 0.79 µg/L (range, 0.1–4.8 µg/L).

(f) Population-based surveys

Yassin & Martonik (2004) calculated the prevalence and mean urinary cadmium levels for all US workers, based on data collected from 11228 US workers aged 18–64 years who participated in the Third National Health and Nutrition Examination Survey (NHANES III, 1988–94). For all workers, urinary cadmium levels were in the range of 0.01–15.57 µg/L, with a geometric mean of 0.30 µg/L (0.28µg/g creatinine). The prevalence of elevated urinary cadmium levels was reported on the basis of the following ranges: ≥ 15 µg/L, ≥ 10 µg/L, ≥ 5 µg/L, and ≥ 3 µg/L. For all US workers aged 18–64 years, the prevalence of urinary cadmium levels ≥ 5 µg/L was 0.42% (n = 551000), for levels ≥ 10 µg/L, 0.06% (n = 78 471), and for levels ≥ 15 µg/L, 0.0028% (n = 3907). The proportion of workers with elevated urinary cadmium varied by occupation and industry. Within industry, urinary

cadmium levels ≥ 10 µg/L were twice as prevalent among workers in the metal industry compared to workers in the manufacturing industry (0.45% versus 0.26%). Within occupation, urinary cadmium levels ≥ 5 µg/L were 12 times as prevalent among vehicle mechanics than in transportation workers (1.71% versus 0.14%), and five times as prevalent in construction workers than in agriculture workers (0.73% versus 0.14%).

1.5.3 Dietary exposure

Low levels of cadmium have been measured in most foodstuffs (average concentrations are less than 0.02 µg/g). Factors influencing cadmium levels in food include: food type (e.g. seafood or leafy vegetables versus meat or dairy), growing conditions (e.g. soil type, water), agricultural and cultivation practices, meteorological conditions (i.e. rate of atmospheric deposition), and anthropogenic contamination of soil or aquatic system (UNEP, 2008; EFSA, 2009; WHO, 2011). Highly contaminated areas have higher cadmium concentrations in locally produced food, and the use of cadmium-containing fertilizers in agriculture increase cadmium concentrations in the crops, and derived products.

High concentrations of cadmium are found in leafy vegetables (e.g. lettuce, spinach), starchy roots (e.g. potatoes), cereals and grains, nuts and pulses (e.g. peanuts, soybeans, sunflower seeds). Lower concentrations of cadmium are found in meat and fish, with the exception of certain shellfish (e.g. oysters), and certain organ meats (e.g. kidney and liver), which concentrate cadmium. Weekly dietary intake estimates in the EU are in the range of 1.9–3.0 µg/kg body weight (mean, 2.3 µg/kg body weight) for non-vegetarians. Vegetarians, regular consumers of bivalve mollusks, and wild mushrooms are, respectively, estimated to have weekly dietary cadmium exposures of 5.4 µg, 4.6 µg, and 4.3 µg (per kg of body weight). On a body weight basis, estimated cadmium intakes are generally higher for infants and children than for adults (UNEP, 2008; EFSA, 2009).

1.5.4 Biomarkers of exposure

Several analytical procedures are available for measuring cadmium concentrations in biological samples. These include: atomic absorption spectroscopy (AAS), electrothermal atomic absorption spectroscopy (ET-AAS), flame atomic absorption, graphite furnace atomic absorption, inductively coupled plasma atomic emission spectroscopy (ICP-AES), inductively coupled plasma mass spectrometry (ICP-MS), neutron activation analysis, potentiometric stripping analysis, radiochemical neutron activation analysis, X-ray fluorescence, and treatment with methyl isobutyl ketone, ammonium pyrrolidenedithiocarbamate, or 13-bis[2-(pyridyl)ethylidene]thiocarbonhydride. The choice of analytical method is determined by several factors, including the sample matrix available (i.e. blood, plasma, serum, tissue, milk, hair, kidney, liver, muscle, urine, or teeth), and the detection limit required (ATSDR, 2008).

Cadmium in blood is used as an indicator of both recent and cumulative exposures, and urinary cadmium predominantly reflects cumulative exposure and the concentration of cadmium in the kidney (CDC, 2005). In the general population, normal blood cadmium concentrations are in the range of 0.4–1.0 µg/L for non-smokers and 1.4–4 µg/L for smokers, although much higher levels have been reported for environmental exposure (above 10 µg/L), and occupational exposure (up to 50 µg/L) (UNEP, 2008). Women typically have higher urinary cadmium concentrations than men, in part perhaps magnified by adjustment for creatinine excretion, which is lower in women (EFSA, 2009).

In a general population survey of approximately 4700 adults in Germany, Becker *et al.* (2002, 2003) found geometric mean cadmium levels of 0.44 µg/L in blood, and 0.23 µg/L in

urine. Smokers had a blood level of 1.1 µg/L, and non-smokers a level of 0.28 µg/L. Smokers had a urine level of 0.29 µg/L, former smokers 0.25 µg/L, and never-smokers 0.18 µg/L.

A study by the Centers for Disease Control and Prevention in the USA based on data from a random sample of people (National Health and Nutrition Examination Survey 1999–2002), found that the mean blood concentration of cadmium was 0.41 µg/L (n = 7970), and the 95th percentile blood concentration was 1.3 µg/L; the mean urine concentration of cadmium was 0.91 µg/L (n = 2257), and the 95th percentile blood concentration was 1.2 µg/L (CDC, 2005). NHANES data for workers in the period 1988–94 (urinary cadmium) are presented in Section 1.5.2 (Yassin & Martonik, 2004).

In an investigation of non-occupational cadmium exposure of 52 adult women in Bangkok, Thailand, Zhang *et al.* (1999) found a geometric mean level of cadmium in blood of 0.41 µg/L and 1.40 µg/g creatinine in urine. These were the lowest when compared to four neighbouring cities in South-eastern Asia (Kuala Lumpur, 0.74 µg/L and 1.51 µg/g; Manila, 0.47 µg/L and 1.21 µg/g; Nanning, 0.71 µg/L and 1.87 µg/g; and Tainan, 0.83 µg/L and 1.59 µg/g).

2. Cancer in Humans

The previous *IARC Monograph* on beryllium and beryllium compounds conclusion was based largely on evidence of increased lung cancer risk among workers exposed to cadmium (IARC, 1993b).

2.1 Cancer of the lung

In two small copper–cadmium alloy plants in the United Kingdom, the rate of mortality from lung cancer was increased in one but decreased in the other (Holden, 1980). The follow-up was extended by Sorahan *et al.* (1995) who documented increased risks of lung cancer in vicinity workers only, and an increased risk of non-malignant diseases of the respiratory system at higher cumulative cadmium exposures [Although an increased risk of lung cancer was not documented in this study, the Working Group noted that cases of lung cancer could potentially be misclassified as non-malignant disease. There was some population overlap between these studies.]

For cadmium-processing workers from 17 plants in the United Kingdom, mortality from lung cancer was significantly increased (standardized mortality ratio [SMR], 1.12; 95%CI: 1.00–1.24), with apparent positive trends with duration of employment and with intensity of exposure (Kazantzis & Blanks, 1992). The increase in lung cancer risk was stronger in the small proportion of workers with high cadmium exposure (SMR, 1.62; 95%CI: 0.89–2.73).

Follow-up of the United Kingdom Ni–Cd battery workers confirmed a slight increase in SMR for lung cancer associated with duration of employment in high-exposure jobs (Sorahan, 1987). Although not associated with cumulative exposure to cadmium, a significant increase in the SMR for cancers of the pharynx was also seen, and a non-significantly increased SMR for lung cancer was observed (Sorahan & Esmen, 2004).

An increase in mortality rates from lung cancer was detected in a small cohort of individuals who worked in the Ni–Cd battery-producing industry in Sweden, and who had the longest duration of employment and latency (Elinder *et al.*, 1985). Further follow-up showed an SMR for lung cancer in male battery workers of 1.76 (95%CI: 1.01–2.87), although without association with estimated total cadmium exposure (Järup *et al.*, 1998).

Excess mortality from lung cancer was reported among workers employed in a US cadmium recovery plant, which had been an arsenic smelter until 1925 (Lemen *et al.*, 1976),

and a dose–response relationship was demonstrated between the estimated cumulative exposure to cadmium and lung cancer risk (Stayner *et al.*, 1993). The dose–response relationship was unlikely to be due to confounding by cigarette smoking, and the relationship persisted among workers employed after 1940, when little arsenic was present in feedstock (Stayner *et al.*, 1993). The US Occupational Safety and Health Administration (OSHA) estimated that exposure to arsenic would have resulted in no more than one case of lung cancer death in this cohort. Using detailed job histories and dust measurements from the same US plant, Sorahan & Lancashire (1997) estimated total cadmium exposure, and identified workers with and without high potential for exposure to arsenic. Relative to the workers in the lowest cumulative exposure category, increased SMRs for lung cancer were found among the workers in higher exposure categories, especially after a lag time of 10 or 20 years. However, significant excess risks of lung cancer were found only for the early years of operation, when exposures to cadmium occurred in the presence of high arsenic exposures. For workers only employed in jobs with little or no exposure to arsenic, cumulative exposure to cadmium was weakly associated with lung cancer mortality. A subsequent analysis of the arsenic-exposed component of this cohort (Sorahan, 2009) showed a statistically significant reduction in risk of lung cancer SMRs in relation to time since leaving employment with arsenic exposure. This pattern was interpreted by the author as implying a late-stage action of arsenic, and a role for arsenic and not cadmium in the causation of lung cancer in this cohort. [The Working Group found this indirect argument against a role for cadmium not to be convincing. The Working Group noted that the population overlapped between these studies.]

In Belgium, Nawrot *et al.* (2006) studied subjects residing near three zinc smelters and also subjects from the area away from the cadmium pollution for the incidence of cancer from initial examinations in 1985–89 to 2004. Using urinary cadmium excretion and cadmium in garden soil as exposure indicators, the hazard ratio for lung cancer was 1.70 (95%CI: 1.13–2.57) for a doubling of the 24-hour urinary cadmium excretion, 4.17 (95%CI: 1.21–14.4) for residence in the high-exposure area versus the low-exposure area, and 1.57 (95%CI: 1.11–2.24) for a doubling of the cadmium concentration in soil. Overall cancer was also increased in the high-exposure group. Information on smoking was included in the adjustments. Data on urinary cadmium excretion adjusted for arsenic suggested that arsenic exposure alone could not explain the observed increases in risk.

See Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-03-Table2.1.pdf

2.2 Cancer of the prostate

Following a report of the occurrence of cancer of the prostate in a small group of workers employed in a plant manufacturing Ni–Cd batteries in the United Kingdom (Potts, 1965), a series of analyses of different occupational cohorts were undertaken, which did not confirm the excess (Kipling & Waterhouse, 1967; Kjellström *et al.*, 1979; Holden, 1980; Sorahan & Waterhouse, 1983; Elinder *et al.*, 1985; Thun *et al.*, 1985; Sorahan, 1987; Kazantzis & Blanks, 1992; Sorahan & Esmen, 2004). Some of these studies reported a non-significantly increased risk for cancer of the prostate among cadmium-exposed workers, but the results were inconsistent, and mostly based on small numbers of cases. Sahmoun *et al.* (2005) calculated a weighted SMR from four studies of Ni–Cd battery production workers who were highly exposed to cadmium. The summary SMR was 1.26 (95%CI: 0.83–1.84) based on 27 deaths. [The Working Group noted that these populations overlapped.] See Table 2.2

available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-03-Table2.2.pdf.

Slightly increased odds ratios for cancer of the prostate were also reported from a case–control study nested within occupational cohorts (Armstrong & Kazantzis, 1985). A hospital-based case–control study using cadmium measurements in toenails (Vinceti *et al.*, 2007) showed a significantly increased odds ratio at the highest concentrations. A case–control study nested within a cohort did not find this association, using the same biological sample collected at baseline as the exposure measure (Platz *et al.*, 2002). [The Working Group noted that the exposure in the second study was lower than in the first, and that the cadmium concentration in toenails may represent a prediagnostic retention level of unknown validity as a measure of long-term exposure.]

A descriptive study from cadmium-polluted areas in Japan reported an increased mortality from cancer of the prostate in two of four areas studied (Shigematsu *et al.*, 1982). Using increased urinary excretion of β_2-microglobulin as a marker of cadmium toxicity within the Nagasaki Prefecture, increased cancer mortality (relative risk [RR], 2.58; 95%CI: 1.25–5.36) and cancer incidence (RR, 1.79; 95%CI: 0.84–3.82) were found among the subjects with signs of cadmium toxicity (Arisawa *et al.*, 2001, 2007). Numbers for individual cancer sites were too low to allow for detailed analysis. [The Working Group noted that these populations overlapped.]

2.3 Other cancers

Other cancer sites, such as the pancreas, show a possible excess in SMRs, but only small numbers of cases have occurred in the occupational cohorts. In a small case–control study, the OR per ng/mL change in serum cadmium concentrations was estimated as 1.12 (95%CI: 1.04–1.23) for cancer of the pancreas (Kriegel *et al.*, 2006). [The Working Group noted that the serum concentration of cadmium is a less valid measure of cadmium exposure than concentrations in urine and whole blood.]

For cancer of the kidney, small numbers were reported in two of the cohort studies without any evidence of an association with cadmium exposure (Järup *et al.*, 1998; Sorahan & Esmen, 2004), but more recent data are available from case–control studies. A German multicentre study (Pesch *et al.*, 2000) included 935 cases of renal cell carcinoma and 4298 controls, and cadmium exposure was assessed by a national job–exposure matrix (JEM). In men and women, respectively, the OR was 1.4 (95%CI: 1.1–1.8) and 2.5 (95%CI: 1.2–5.3) for high exposure and 1.4 (95%CI: 0.9–2.1) and 2.2 (95%CI: 0.6–9.0) for very high exposure. In a Canadian study of 1279 cases of renal cell carcinoma and 5370 controls, self-reported cadmium exposure was a risk factor in males (OR, 1.7; 95%CI: 1.0–3.2) (Hu *et al.*, 2002). Most recently, a German hospital-based case–control study of 134 cases of renal cell carcinoma and 401 controls reported an OR for high exposure of 1.7 (95%CI: 0.7–4.2) (Brüning *et al.*, 2003).

A hypothesis-generating case–control study in the Montréal (Canada) metropolitan area showed that the bladder was the only one of 20 cancer sites to be associated with exposure to cadmium compounds (Siemiatycki, 1991). In a case–control study of transitional cell carcinoma of the bladder, the blood cadmium concentration was measured as an indicator of long-term cadmium exposure; the highest exposure tertile showed an OR of 5.7 (95%CI: 3.3–9.9); adjustments included smoking and occupational exposures to polyaromatic hydrocarbons and aromatic amines (Kellen *et al.*, 2007).

In another study, increased cadmium concentrations were found in breast tissue, but the mean cadmium concentration found in breast cancer patients was not significantly different from that of controls (Antila *et al.*, 1996). A larger case–control study of breast cancer used urinary cadmium excretion levels as a measure

of cumulated cadmium exposure; each increase by 1.0 µg/g creatinine was associated with an OR of 2.09 (95%CI: 1.2–3.8) (McElroy *et al.*, 2006).

On the basis of food frequency questionnaires in 1987–90 and 1997, Åkesson *et al.* (2008) calculated dietary cadmium intakes; the highest tertile of cadmium exposure had an OR of 1.39 [95%CI: 1.04–1.86] for endometrial cancer in postmenopausal women. The association was stronger in never-smokers, in women with normal body mass index, and in non-users of postmenopausal hormones.

2.4 Synthesis

The assessment of cancer risks in occupational cohorts exposed to cadmium is constrained by the small number of long-term, highly exposed workers, the lack of historical data on exposure to cadmium, particularly for the non-US plants, and the inability to define and examine a gradient of cumulative exposure across studies. Confounding by cigarette smoking in relation to the assessment of lung cancer risk among cadmium-exposed workers was addressed directly only in the study from the USA. Some other studies provided analyses based on internal comparisons, which are not likely to be affected by this problem of confounding. Few studies were able to control the confounding effect of co-exposure to other substances, particularly arsenic and nickel; however, the analyses of workers with low levels of exposure to arsenic still showed an increased lung cancer risk associated with cadmium exposure. Additional support for a cadmium-linked lung cancer risk comes from a prospective population-based study in environmentally polluted areas in Belgium.

The results of the studies on cadmium exposure and the risk of prostate cancer are suggestive of an association, but the results are inconsistent. In studies of occupational cohorts exposed to cadmium, studies of people residing in cadmium-contaminated areas and case–control studies of individuals with prostate cancer, some studies reported an increased risk for prostate cancer, while other studies did not indicate the same. The results from cohort studies are supported by a hospital-based case–control study that included highly exposed subjects.

Case–control studies suggest that other cancer sites, such as the kidney, and perhaps also the bladder, the breast, and the endometrium may show increased risks associated with dietary or respiratory cadmium exposure. [The Working Group noted that although case–control studies may be subject to bias from exposure misclassification, some studies considered have the strength of inclusion of blood or urine cadmium analyses that provide individual exposure data.]

3. Cancer in Experimental Animals

Cadmium compounds have been tested for carcinogenicity by subcutaneous administration to rats, mice, and hamsters, by intramuscular injection to rats, by oral exposure to rats and mice, by intraperitoneal exposure to mice, by inhalation exposure to rats, mice and hamsters, and by intratracheal administration to rats.

Particularly relevant studies reviewed in the previous *IARC Monograph* (IARC, 1993b) were reconsidered in this evaluation.

All cadmium compounds tested were not carcinogenic by all routes tested but most studies performed provided evidence for cadmium-induced carcinogenicity in animals.

3.1 Oral administration

Oral administration of cadmium chloride to rats increased the incidence of large granular lymphocytes, leukaemia, prostate tumours, and testis tumours in Wistar rats (Waalkes & Rehm, 1992). Noble rats exposed to oral cadmium chloride developed prostate hyperplasia (Waalkes *et al.*, 1999b).

See Table 3.1.

Table 3.1 Studies of cancer in experimental animals exposed to cadmium (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar WF/NCr (M) 77 wk Waalkes & Rehm (1992)	Cadmium chloride 0, 25, 50, 100 or 200 ppm in diet Also fed previous diets with zinc levels of 60 ppm (zinc adequate), 7 ppm (zinc deficient) for 2 wk 28/group 56 pooled controls	Prostate (tumours): 4/26 (15%) cadmium (50ppm) vs 1/54 (2%) pooled controls High-dose cadmium + zinc deficient: Testis (tumours)– 6/27 (22%) vs 1/28 (3%) controls Leukaemia (LGL): 7/25 (28%) vs pooled controls 3/55 (5%)	$P < 0.05$ $P < 0.05$	Age at start, 2 wk Prostate tumours not affected by zinc deficiency unless combined with prostate hyperplasias No increase in testis tumours with cadmium alone
Rat, Noble NBL/Cr (M) 102 wk Waalkes *et al.* (1999b)	Cadmium chloride 0, 25, 50, 100, 200 ppm in drinking-water 30/group	Prostate (dorsolateral and ventral; hyperplasias): 6 (21%), 12 (46%), 13 (50%), 6 (21%), 4 (15%) Testis (tumours): 2/29 (7%), 2/30 (7%), 3/30 (10%), 4/30 (13%), 5/28 (18%) Adrenal gland (pheochromocytomas): 2 (7%), 3 (10%), 8 (27%), 6 (20%), 3 (10%)	$P < 0.05$ vs control (Groups 2 & 3) NR $P < 0.05$ (mid-dose)	Age at start, 10 wk No dose response to induction of any tumour type

d, day or days; h, hour or hours; mo, month or months; LGL, large granular lymphocyte; NR, not reported; NS, not significant; vs, versus; wk, week or weeks

3.2 Inhalation and intratracheal administration

3.2.1 Rat

Inhalation exposure to cadmium chloride caused lung tumours in rats (Takenaka *et al.*, 1983; Glaser *et al.*, 1990). Cadmium sulfate, cadmium oxide, cadmium oxide fume and dust also caused lung tumours in rats (Glaser *et al.*, 1990).

Intratracheal administration of cadmium chloride and cadmium sulfide caused lung tumours in rats (Oberdörster & Cherian, 1992).

3.2.2 Hamster

Cadmium chloride, cadmium sulfate, cadmium sulfide, and cadmium oxide fume did not cause lung tumours in hamsters (Heinrich *et al.*, 1989; Heinrich, 1992).

See Table 3.2.

3.3 Subcutaneous administration

Many of the earliest carcinogenicity studies with cadmium compounds in rodents involved subcutaneous or intramuscular administration. In most studies, injection-site sarcomas developed in rats and mice. Mice were generally less susceptible than were rats. The earlier studies are reviewed in the previous *IARC Monograph*, and are not reviewed here, in part, because larger and better designed studies were published after 1993.

3.3.1 Mouse

Subcutaneous administration of cadmium chloride caused lymphomas, lung tumours (Waalkes & Rehm, 1994), and injection-site sarcomas (Waalkes *et al.*, 1991a; Waalkes & Rehm, 1994) in mice.

3.3.2 Rat

Subcutaneous administration of cadmium chloride caused injection-site sarcomas (Waalkes *et al.*, 1988, 1989, 1991b, 1997, 1999a, 2000; IARC, 1993b; Shirai *et al.*, 1993), and testis (interstitial cell) tumours in rats (Waalkes *et al.*, 1988, 1989, 1997, 1999b, 2000). Cadmium chloride caused prostate tumours and/or preneoplastic lesions in Wistar and Noble rats (Waalkes *et al.*, 1988, 1999b), but not in other studies in F344 or Wistar Furth rats (Waalkes *et al.*, 1991c, 2000; Shirai *et al.*, 1993).

3.3.3 Hamster

A single injection of cadmium chloride did not induce tumours in hamsters (Waalkes & Rehm, 1998).

A variety of cadmium compounds and metallic cadmium caused local sarcomas in rats or mice (IARC, 1993b).

See Table 3.3.

3.4 Administration with known carcinogens or other agents

The incidence of injection-site sarcomas in Wistar rats induced by cadmium chloride was significantly reduced by both the subcutaneous and oral administration of zinc (Waalkes *et al.*, 1989). Testicular tumours induced by subcutaneously administered cadmium chloride were inhibited by zinc, and were found to be associated with a reduction of the chronic degenerative testicular lesions induced by cadmium chloride (Waalkes *et al.*, 1989).

Testosterone implantation eliminated both cadmium-induced and spontaneous testis tumours in F344 rats but had no effect on cadmium-induced chronic testicular degeneration (Waalkes *et al.*, 1997).

Table 3.2 Studies of cancer in experimental animals exposed to cadmium (inhalation and intratracheal exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Inhalation				
Rat, Wistar, TNO/W75 (M) 31 mo Takenaka *et al.* (1983)	Cadmium chloride 12.5, 25 or 50 µg/m^3, 23 h/d, 7 d/wk for 18 mo 40/group	Lung (adenocarcinomas): 0/38, 6/39 (15%), 20/38 (52%), 25/35 (71%)	[$P < 0.0001$; Groups 3 & 4]	Age at start, 6 wk
Rat, Wistar, TNO/W75 > BOR-WISW (M, F) 31 mo Glaser *et al.* (1990)	0 to 900 µg/m^3 of cadmium chloride, cadmium sulfate, cadmium oxide, cadmium oxide fume, zinc oxide dust, and cadmium oxide dust, 40 h/wk for 18 mo Groups of 20–40 males, 20 females	All forms increased lung tumour incidence, 18/20 (90%) in cadmium sulfate females, 0/20 in controls from 31 experimental groups Controls, males 0/40, females 0/20 High doses > 75% incidences	[$P < 0.0001$]	Age at start, 9 wk Problem with concentration of cadmium in cadmium oxide fume Data from 31 experimental groups in Table 13, p.166, Volume 58 (IARC, 1993b)
Intratracheal				
Rat, Wistar (F) 124 wk Oberdörster & Cherian (1992)	Cadmium chloride or cadmium oxide 20 weekly 1 or 3 µg or 15 weekly 9 µg Cadmium sulfide 10 weekly 63, 250 or 1000 µg (purity 99%) Controls received 20x0.3ml saline	Lung (tumours): Cadmium chloride– Controls, 0/40; 20, 0/38; 60, 3/40 (7%); 135, 2/36 (6%) Cadmium oxide– 20, 2/37 (5%); 60, 2/40 (5%); 135, 0/39 Cadmium sulfide– 630, 2/39 (5%); 2500, 8/36 (22%); 10000, 7/36 (19%)	$P < 0.01$ trend test NS $P = 0.0005$ trend test	Cadmium chloride and cadmium sulfide purity, 99%

d, day or days; h, hour or hours; mo, month or months; NR, not reported; NS, not significant; wk, week or weeks

Table 3.3 Studies of cancer in experimental animals exposed to cadmium (subcutaneous or intramuscular exposure; for years < 1993, only selected references included)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar Crl WI BR (M) 104 wk Waalkes *et al.* (1988)	Cadmium chloride Single s.c. 0, 1, 2.5, 5, 10, 20, or 40 µmol/kg bw; 5 µmol/kg 4 × 5 and 10 µmol/kg 1 × each, 5 and 20 µmol/kg 1 × each (time 0 (low dose) and 48 h (high dose)) 30/group 45 pooled controls	Injection site (mostly sarcomas, also fibromas, epithelial tumours): 2/45 (4%), 1/30 (3%), 0/29, 1/30 (3%), 2/30 (7%), 1/29 (3%), *14/30 (47%) 0/30, 1/30 (3%), *8/30 (27%) Testis (tumours): 8/45 (18%), 1/30 (3%), 3/29 (10%), 3/30 (10%), 4/30 (13%), *21/29 (72%), *24/29 (83%) 4/30 (13%), 2/30 (7%), 5/30 (17%) Prostate (ventral lobe; tumours): 5/44 (11%), 6/27 (22%), *8/26 (31%), 4/28 (14%), 4/23 (17%), 4/26 (15%), 3/29 (10%) 2/26 (8%), 5/28 (18%), 6/28 (21%) Preneoplastic foci: Positive trend with single dose (data in chart) Pancreas (acinar and islet cell): Negative trend with dose	$P < 0.05$ from pooled control $P < 0.05$ $P < 0.05$ from pooled control NR NR	Age at start, 6 wk High dose cadmium reduced testicular tumour responses Prostate tumour response is not strong or a dose response

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar (M) 104 wk Waalkes *et al.* (1989)	Cadmium chloride Single injection s.c. 30 µmole/kg 3 × zinc acetate 0.1, 0.3, 1.0 mmol/kg i.m. 30 mmole/kg cadmium chloride + zinc chloride 1 mmol/kg + zinc acetate in water 30/group	Injection site (sarcomas): 12/30 (40%), pooled controls 0/84 1 × zinc reduced incidence Testis (tumours): Cd 1 × 25/30 (83%), controls 9/83 (11%) Zinc, dose-dependent decrease Prostate (adenoma): i.m. Cd 11/26 (42%), Cd+zinc 8/27 (30%), i.m. Cd+s.c. zinc 7/28 (25%), controls 8/83 (10%)	$P < 0.05$ $P < 0.05$ $P < 0.05$	
Rat, F344 (M) 104 wk Waalkes *et al.* (1997)	Cadmium chloride 20 µmole/kg s.c. once/wk for 5 wk Testosterone implants, 10 interim sacrifices 50/group	Testis (tumours): Controls 24/40 (60%) Testosterone only *0/40 Cd only *34/40 (98%) Testosterone+Cd *†0/37	*$P \leq 0.05$ from control †$P \leq 0.05$ from cadmium alone	Age at start, 10 wk
Rat, Noble, NBL/Cr (M) 72 wk Waalkes *et al.* (1999a)	Cadmium chloride Single injection s.c. 0, 1, 2, 4, 8, 16, 32 µmole/kg 30/group	Testis: 1/30 (3%), 0/30, 0/30, 1/30 (3%), 7/30 (23%), 29/30 (96%), 28/30 (93%) Injection site (sarcomas): 0/30, 0/30, 0/30, 0/30, 0/30, 0/30, 7/30 (22%), 11/30 (37%) Prostate (proliferative lesions): 9/25 (36%), 16/26 (62%), 19/29 (65%), 19/24 (79%), 17/27 (63%), 18/30 (60%), 15/29 (52%)	$P < 0.053$ (higher doses) $P < 0.05$ $P < 0.05$, three middle doses	Prostate hyperplasia only

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, WF/NCr, F344/NCr (M) 104 wk Waalkes *et al.* (2000)	Cadmium chloride Single injection, s.c. 0, 10, 20, 30 µmole/kg bw weekly for 18 wk, 3 µmole/kg 1 wk then weekly 17 × 30 µmole/kg 30/group	Injection site (sarcomas): WF–0/20, 1/29 (3%), 21/29 (72%), 23/28 (82%), 23/29 (79%) F344–0/30, 11/30 (37%), 17/30 (68%), 8/12 (67%), 18/30 (60%)	$P < 0.05$ WF, four highest doses; F344 all doses	No prostate tumours were reported
		Testis: WF–11/29 (38%), 27/29 (93%), 19/29 (65%), 15/28 (54%), 15/29 (52%) F344–29/30 (97%), 28/30 (93%), 14/25 (56%), 8/12 (67%), 12/30 (43%)	$P < 0.05$ WF, two lower doses; F344 reduction in three highest doses	Pituitary adenomas reduced in higher doses of WF rats
Mouse, DBA/2NCr, NFS/NCr 104 wk (Waalkes & Rehm, 1994)	Cadmium chloride 40 µmol/kg s.c. 1once or once/wk for 16 wk 30–40/group	Lymphomas: DBA–1X Cd, 11/23 (48%); 16 × Cd, *16/28 (57%) Controls, 7/27 (26%)	$P = 0.024$ trend test	Age, 8 wk Strain differences seen No testis tumours
		Injection site (sarcomas): NFS–1X Cd, 3/27 (11%); 16 × Cd, 3/32 (9%) Controls, 0/23	$P = 0.016$ trend test	
		Lung: NFS–1X Cd, *21/28 (75%); 16 × Cd, 9/35 (26%) Controls, 6/25 (24%)		

h, hour or hours; i.m., intramuscular; NR, not reported; s.c., subcutaneous; wk, week or weeks

3.5 Synthesis

By inhalation, various cadmium compounds induce lung tumours in rats (cadmium chloride, cadmium oxide, cadmium oxide dust, cadmium oxide fumes, cadmium sulfide). Intratracheal administration of cadmium chloride and cadmium sulfide induces lung tumours in rats. In one study, subcutaneous injection of cadmium chloride caused lung tumours in mice. A variety of cadmium compounds and metallic cadmium cause local sarcomas in rats or mice. Administration of various salts of cadmium causes testicular tumours in rats. Cadmium chloride induced prostatic proliferative lesions and testicular tumours in rats after subcutaneous or oral administration.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

Inhalation is the major route of cadmium exposure in occupational settings, whereas most people in the general population are exposed to cadmium via the ingestion of both food and drinking-water. Exposure to cadmium particulates lead to cadmium absorption in animals and humans (IARC, 1993b).

In occupational settings, cadmium and cadmium compounds, being non-volatile, exist in air as fine particulates. Animal studies (Rusch *et al.*, 1986) have shown that lung retention may be up to 20%, especially after short-term exposure.

When ingested, most of the cadmium passes through the gastrointestinal tract without being absorbed. Estimates of the cadmium absorption rate in humans have been reported as 3–5% (Morgan & Sherlock, 1984) or 6.5% (Horiguchi *et al.*, 2004). Even lower rates have been reported for experimental animals, especially after long-term repeated exposures (Schäfer *et al.*, 1990).

When absorbed, cadmium will bind to metallothionein, forming a cadmium–metallothionein complex that is transferred (via blood) primarily to the liver and the kidney (Waalkes & Goering, 1990). Metallothionein is inducible in different tissues (e.g. liver, kidney, intestine, and lung) by exposure to various agents including cadmium (Waalkes & Goering, 1990). When transported to the kidney, cadmium–metallothionein is readily filtered at the glomerulus, and may be efficiently reabsorbed from the filtrate in the proximal tubules (Foulkes, 1978; Dorian *et al.*, 1992a). In the tubules, the protein portion is rapidly degraded to release cadmium (Dorian *et al.*, 1992b). Cadmium accumulates in kidney tubules, and causes damage to tubular cells, especially in the proximal tubules (Kasuya *et al.*, 1992).

Absorbed cadmium is excreted very slowly, and the amounts excreted into urine and faeces are approximately equal (Kjellström & Nordberg, 1978). In humans, half-life estimates are in the range of 7–16 years (Kjellström & Nordberg, 1978; Nordberg *et al.*, 2007).

4.2 Genetic and related effects

In rodent experiments, cadmium salts cause increased frequencies of micronuclei and chromosomal aberrations. In mammalian cells *in vitro*, cadmium compounds cause DNA strand breaks and chromosomal aberrations, and are weakly mutagenic, whereas in most bacterial assays, cadmium compounds are not mutagenic (Waalkes, 2003; DFG, 2006). Both soluble and insoluble cadmium compounds generally give comparable results in genotoxicity assays when tested in parallel.

Because cadmium salts do not cause DNA damage in cell extracts or with isolated DNA (Valverde *et al.*, 2001), the genotoxicity of cadmium has to be explained by indirect mechanisms. Frequently discussed mechanisms are related to oxidative stress, the inhibition of

DNA-repair systems, effects on cell proliferation, and on tumour-suppressor functions.

4.2.1 Induction of oxidative stress

Even though cadmium is not redox-active, it has been shown to induce oxidative stress, both *in vitro* and *in vivo*. Cadmium sulfide induced hydrogen peroxide formation in human polymorphonuclear leukocytes, and cadmium chloride enhanced the production of superoxide in rat and human phagocytes (Sugiyama, 1994). The induction of DNA strand breaks and chromosomal aberrations by cadmium in mammalian cells is suppressed by antioxidants and antioxidative enzymes (Ochi *et al.*, 1987; Stohs *et al.*, 2001; Valko *et al.*, 2006). Because cadmium does not undergo redox reactions under physiological conditions, the increased generation of reactive oxygen species levels and oxidative cellular damage may be due to the inhibitory effect of cadmium on antioxidant enzymes (Stohs *et al.*, 2001; Valko *et al.*, 2006) as well as on DNA-repair systems.

4.2.2 Inhibition of DNA repair

Cadmium is co-mutagenic and increases the mutagenicity of ultraviolet radiation, alkylation, and oxidation in mammalian cells. These effects are explained by the observation that cadmium inhibits several types of DNA-repair mechanisms, i.e. base excision, nucleotide excision, mismatch repair, and the elimination of the pre-mutagenic DNA precursor 7,8-dihydro-8-oxoguanine (Hartwig & Schwerdtle, 2002). In base-excision repair, low concentrations of cadmium that do not generate oxidative damage as such, very effectively inhibit the repair of oxidative DNA damage in mammalian cells (Dally & Hartwig, 1997; Fatur *et al.*, 2003). In nucleotide-excision repair, cadmium interferes with the removal of thymine dimers after UV irradiation by inhibiting the first step of this repair pathway, i.e. the incision at the DNA lesion (Hartwig & Schwerdtle, 2002; Fatur *et al.*, 2003). Furthermore, chronic exposure of yeast to very low cadmium concentrations results in hypermutability; and in human cell extracts, cadmium has been shown to inhibit DNA-mismatch repair (Jin *et al.*, 2003). Additionally, cadmium disturbs the removal of 8-oxo-dGTP from the nucleotide pool by inhibiting the 8-oxo-dGTPases of bacterial and human origin (Bialkowski & Kasprzak, 1998).

One molecular mechanism related to the inactivation of DNA-repair proteins involves the displacement by cadmium of zinc from zinc-finger structures in DNA-repair proteins such as xeroderma pigmentosum group A (XPA), which is required for nucleotide-excision repair, and formamidopyrimidine-DNA-glycosylase (Fpg), which is involved in base-excision repair in *E. coli* (Asmuss *et al.*, 2000). Cadmium also inhibits the function of human 8-oxoguanine-DNA-glycosylase (hOGG1), which is responsible for recognition and excision of the pre-mutagenic 7,8-dihydro-8-oxoguanine during base-excision repair in mammalian cells (Potts *et al.*, 2003). Even though hOGG1 contains no zinc-binding motif itself, the inhibition of its function is due to its downregulation as a result of diminished DNA-binding of the transcription factor SP1 that contains zinc-finger structures (Youn *et al.*, 2005). Finally, cadmium induces a conformational shift in the zinc-binding domain of the tumour-suppressor protein p53. Thus, in addition to inhibiting repair proteins directly, cadmium downregulates genes involved in DNA repair *in vivo* (Zhou *et al.*, 2004).

The impact of cadmium on DNA repair may be especially deleterious in cadmium-adapted cells. Cadmium induces several genes for cadmium and reactive oxygen species tolerance such as those coding for metallothionein, glutathione synthesis and function, catalase and superoxide dismutase (Stohs *et al.*, 2001). Hence, a condition for prolonged cell survival in the

presence of cadmium is established (Chubatsu *et al.*, 1992). Taking into account the impact of cadmium on DNA repair, tolerance to cadmium toxicity concurrently may constitute a greater opportunity for the induction of further critical mutations (Achanzar *et al.*, 2002).

4.2.3 Deregulation of cell proliferation and disturbance of tumour-suppressor functions

Cadmium interacts with a multitude of cellular signal transduction pathways, many of which associated with mitogenic signalling. Submicromolar concentrations of cadmium stimulated DNA synthesis, and the proliferation of rat myoblast cells (von Zglinicki *et al.*, 1992) and of rat macrophages (Misra *et al.*, 2002). In various cell types *in vitro*, cadmium induces the receptor-mediated release of the second messengers inositol-1,4,5-trisphosphate and calcium, activates various mitogenic protein kinases, transcription and translation factors, and induces the expression of cellular proto-oncogenes, *c-fos*, *c-myc*, and *c-jun* (Waisberg *et al.*, 2003). However, it should be noted that the activation of mitogen-activated protein kinases is not a sufficient condition for enhanced cell proliferation, because persistent low-dose exposure of cells to cadmium has been shown to result in sustained activation of protein kinase ERK, but also to caspase activation and apoptosis (Martin *et al.*, 2006). In addition to directly stimulating mitogenic signals, cadmium also inhibits the negative controls of cell proliferation. It inactivates the tumour-suppressor protein p53, and inhibits the p53 response to damaged DNA (Méplan *et al.*, 1999). This finding could be particularly important to explain the carcinogenicity of cadmium because p53 is required for cell-cycle control, DNA repair, and apoptosis; its inactivation would be expected to lead to genomic instability.

It was also reported that cadmium modulates steroid-hormone-dependent signalling in ovaries in rats, in a breast cancer cell line, and in cadmium-transformed prostate epithelial cells (Benbrahim-Tallaa *et al.*, 2007a; Brama *et al.*, 2007). Nevertheless, in in-vitro estrogenicity assays based on estrogen-receptor activity, no effect of cadmium was detected (Silva *et al.*, 2006). Whether or not cadmium promotes tumour growth by an estrogen-mediated mechanism is still unknown.

In addition to effects on genes and genetic stability, cadmium also exerts epigenetic effects, which may contribute to tumour development. During cadmium-induced cellular transformation, DNA–(cytosine-5) methyltransferase activity and global DNA methylation were reduced after 1 week of exposure to cadmium (Takiguchi *et al.*, 2003). Prolonged exposure to cadmium (~10 weeks) resulted in enhanced DNA–methyltransferase activity, and global DNA hypermethylation in these cells (Takiguchi *et al.*, 2003), and in human prostate epithelial cells (Benbrahim-Tallaa *et al.*, 2007b). Changes in DNA methylation is thought to have a tumour-promoting effect because a decrease in DNA methylation is associated with increased expression of cellular proto-oncogenes, and an increase of DNA methylation results in the silencing of tumour-suppressor genes.

4.3 Synthesis

Several mechanisms have been identified that potentially contribute to cadmium-induced carcinogenesis. Direct binding to DNA appears to be of minor importance, and mutagenic responses are weak. Convincing evidence exists on disturbances of DNA-repair and tumour-suppressor proteins, which lead to chromosomal damage and genomic instability. Further reported effects include changes in DNA-methylation patterns as well as interactions with signal-transduction processes, which may contribute to the deregulation of cell growth. However, it is not yet possible to assess the relative contributions of these latter mechanisms for cancer in humans.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of cadmium and cadmium compounds. Cadmium and cadmium compounds cause cancer of the lung. Also, positive associations have been observed between exposure to cadmium and cadmium compounds and cancer of the kidney and of the prostate.

There is *sufficient evidence* in experimental animals for the carcinogenicity of cadmium compounds.

There is *limited evidence* in experimental animals for the carcinogenicity of cadmium metal.

Cadmium and cadmium compounds are *carcinogenic to humans (Group 1).*

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CHROMIUM (VI) COMPOUNDS

Chromium (VI) compounds were considered by previous IARC Working Groups in 1972, 1979, 1982, 1987, and 1989 (IARC, 1973, 1979, 1980, 1982, 1987, 1990). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms, trade names, and molecular formulae for selected chromium (VI) compounds are presented in Table 1.1. This list is not exhaustive, nor does it necessarily reflect the commercial importance of the various chromium-containing substances. Rather, it is indicative of the range of chromium (VI) compounds available.

1.2 Chemical and physical properties of the agents

Chromium (VI), also known as hexavalent chromium, is the second most stable oxidation state of chromium. Rarely occurring naturally, most chromium (VI) compounds are manufactured (products or by-products). Chromium (VI) can be reduced to the more stable chromium (III) in the presence of reducing agents (e.g. iron) or oxidizable organic matter (OSHA, 2006). Selected chemical and physical properties of various chromium (VI) compounds are presented in the previous *IARC Monograph* (IARC, 1990).

Chromium (VI) compounds are customarily classed as soluble or insoluble in water. Examples of water-soluble chromium (VI) compounds are sodium chromate (873 g/L at 30 °C) and potassium chromate (629 g/L at 20 °C). Water-insoluble chromium (VI) compounds include barium chromate (2.6 mg/L at 20 °C), and lead chromate (0.17 mg/L at 20 °C) (Lide, 2008). Compounds with solubilities in the middle of this range are not easily classified, and technical-grade compounds, such as the various zinc chromates, can have a wide range of solubilities (IARC, 1990). In the United States of America, the Occupational Safety and Health Administration (OSHA) has divided chromium (VI) compounds and mixtures into the following three categories: water-insoluble (solubility < 0.01 g/L), slightly soluble (solubility 0.01 g/L–500 g/L), and, highly water-soluble (solubility ≥ 500 g/L) (OSHA, 2006).

Chromium (VI) compounds are mostly lemon-yellow to orange to dark red in colour. They are typically solid (i.e. crystalline, granular, or powdery) although one compound (chromyl chloride) is a dark red liquid that decomposes into chromate ion and hydrochloric acid in water (OSHA, 2006).

Table 1.1 Chemical names (CAS names are given in italics), synonyms, and molecular formulae of selected chromium (VI) compounds

Chemical name	CAS No.[a]	Synonyms	Formula[b]
Ammonium chromate	7788-98-9	Chromic acid, ammonium salt; *chromic acid (H_2CrO_4), diammonium salt*; diammonium chromate	$(NH_4)_2CrO_4$
Ammonium dichromate	7789-09-5	Ammonium bichromate; ammonium chromate; *chromic acid ($H_2Cr_2O_7$), diammonium salt*; diammonium dichromate; dichromic acid, diammonium salt	$(NH_4)_2Cr_2O_7$
Barium chromate	10294-40-3 (12000-34-9; 12 231-18-4)	Barium chromate (VI); barium chromate (1:1); barium chromate oxide; *chromic acid (H_2CrO_4), barium salt (1:1)*	$BaCrO_4$
Basic lead chromate	1344-38-3 (54692-53-4)	C.I. 77 601; *C.I. Pigment Orange 21*; C.I. Pigment Red; lead chromate oxide	$PbO.PbCrO_4$
Calcium chromate	13765-19-0	Calcium chromium oxide; calcium monochromate; *chromic acid (H_2CrO_4), calcium salt (1:1)*; C.I. 77223; C.I. Pigment Yellow 33	$CaCrO_4$
Chromium [VI] chloride	14986-48-2	Chromium hexachloride; *(OC-6–11)-chromium chloride ($CrCl_6$)*	$CrCl_6$
Chromium trioxide	1333-82-0 (12324-05-9; 12324-08-2)	Chromia; chromic acid; chromic (VI) acid; chromic acid, solid; chromic anhydride; chromic trioxide; *chromium oxide (CrO3)*; chromium (VI) oxide; chromium (6+) trioxide; monochromium trioxide	CrO_3
Chromyl chloride	14977-61-8	Chlorochromic anhydride; chromium chloride oxide; chromium dichloride dioxide; *chromium, dichlorodioxo-(T-4)*; chromium dioxide dichloride; chromium dioxychloride; chromium oxychloride; dichlorodioxochromium	CrO_2Cl_2
Lead chromate	7758-97-6 (8049-64-7) 1344-37-2	*Chromic acid (H_2CrO_4), lead (2+) salt (1:1)*; C.I. 77600; C.I. Pigment Yellow 34; Chrome Yellow; lead chromate/lead sulfate mixture	$PbCrO_4$
Molybdenum orange	12656-85-8	*C.I. Pigment Red 104*; lead chromate molybdate sulfate red	$PbMoO_4$ $PbCrO_4$ $PbSO_4$
Potassium chromate	7789-00-6	Bipotassium chromate; *chromic acid (H_2CrO_4), dipotassium salt*; dipotassium chromate; dipotassium monochromate; neutral potassium chromate; potassium chromate (VI)	K_2CrO_4
Potassium dichromate	7778-50-9	*Chromic acid ($H_2Cr_2O_7$), dipotassium salt*; dichromic acid, dipotassium salt; dipotassium bichromate; dipotassium dichromate; potassium bichromate; potassium dichromate (VI)	$K_2Cr_2O_7$
Sodium chromate	7775-11-3	*Chromic acid (H_2CrO_4), disodium salt*; chromium disodium oxide; chromium sodium oxide; disodium chromate; neutral sodium chromate; sodium chromium oxide	Na_2CrO_4

Table 1.1 (continued)

Chemical name	CAS No.[a]	Synonyms	Formula[b]
Sodium dichromate	10588-01-9 (12018-32-5)	Bichromate of soda; *chromic acid ($H_2Cr_2O_7$), disodium salt*; chromium sodium oxide; dichromic acid, disodium salt; disodium dichromate; sodium bichromate; sodium dichromate (VI)	$Na_2Cr_2O_7$
Strontium chromate	7789-06-2 (54322-60-0)	*Chromic acid (H_2CrO_4), strontium salt (1:1)*; C.I. Pigment Yellow 32; strontium chromate (VI); strontium chromate (1:1)	$SrCrO_4$
Zinc chromate[c]	13530-65-9 (1308-13-0; 1328-67-2; 14675-41-3)	*Chromic acid (H_2CrO_4), zinc salt (1:1)*; chromium zinc oxide; zinc chromium oxide; zinc tetraoxychromate; zinc tetroxychromate	$ZnCrO_4$
Zinc chromate hydroxides	15930-94-6 (12206-12-1; 66516-58-3)	Basic zinc chromate; chromic acid (H_6CrO_6), zinc salt (1:2); chromic acid (H_4CrO_5), zinc salt (1:2), monohydrate; chromium zinc hydroxide oxide; zinc chromate hydroxide; zinc chromate (VI) hydroxide; *zinc chromate oxide ($Zn_2(CrO_4)O$), monohydrate*; zinc hydroxychromate; zinc tetrahydroxychromate; zinc yellow[d]	$Zn_2CrO_4(OH)_2$ and others
Zinc potassium chromates (hydroxides)	11103-86-9 (12527-08-1; 37809-34-0)	Basic zinc potassium chromate; chromic acid ($H_6Cr_2O_9$), potassium zinc salt (1:1:2); *potassium hydroxyoctaoxodizincate dichromate (1-)*; potassium zinc chromate hydroxide; zinc yellow[d]	$KZn_2(CrO_4)_2(OH)$ and others

[a] Replaced CAS Registry numbers are given in parentheses.

[b] Compounds with the same synonym or trade name can have different formulae.

[c] The term 'zinc chromate' is also used to refer to a wide range of commercial zinc and zinc potassium chromates.

[d] 'Zinc yellow' can refer to several zinc chromate pigments; it has the CAS No. 37300-23-5.

1.3 Use of the agents

Chromium (VI) compounds are used widely in applications that include: pigment for textile dyes (e.g. ammonium dichromate, potassium chromate, sodium chromate), as well as for paints, inks, and plastics (e.g. lead chromate, zinc chromate, barium chromate, calcium chromate, potassium dichromate, sodium chromate); corrosion inhibitors (chromic trioxide, zinc chromate, barium chromate, calcium chromate, sodium chromate, strontium chromate); wood preservatives (chromium trioxide); metal finishing and chrome plating (chromium trioxide, strontium chromate), and leather tanning (ammonium dichromate). Chromium (VI) may be present as an impurity in Portland cement, and it can be generated and given off during casting, welding, and cutting operations (for example, of stainless steel), even if it was not originally present in its hexavalent state (NTP, 2005; OHCOW, 2005; OSHA, 2006).

1.4 Environmental occurrence

Chromium (VI) can occur naturally in the earth's crust, although it is primarily emitted to the environment as a result of anthropogenic activities. The occurrence and distribution of chromium in the environment has been extensively reviewed (Mukherjee, 1998; Kotaś & Stasicka, 2000; Rowbotham *et al.*, 2000; Ellis *et al.*, 2002; Paustenbach *et al.*, 2003; Guertin *et al.*, 2004; Reinds *et al.*, 2006; Krystek & Ritsema, 2007).

1.4.1 Natural occurrence

Only lead chromate (as crocoite) and potassium dichromate (as lopezite) are known to occur in nature (IARC, 1990).

1.4.2 Air

Chromium (VI) is reported to account for approximately one third of the 2700–2900 tons of chromium emitted to the atmosphere annually in the USA (ATSDR, 2008a). Based on US data collected from 2106 monitoring stations during 1977–84, the arithmetic mean concentrations of total chromium in the ambient air (urban, suburban, and rural) were in the range of 0.005–0.525 μg/m^3 (ATSDR, 2000).

1.4.3 Water

The concentration of chromium in uncontaminated waters is extremely low (< 1 μg/L or < 0.02 μmol/L). Anthropogenic activities (e.g. electroplating, leather tanning) and leaching of wastewater (e.g. from sites such as landfills) may cause contamination of the drinking-water (EVM, 2002). Chromium (VI) has been identified in surface water (n = 32) and groundwater samples (n = 113) collected from 120 hazardous waste sites in the USA (ATSDR, 2000), and 38% of municipal sources of drinking-water in California, USA, reportedly have levels of chromium (VI) greater than the detection limit of 1 μg/L (Sedman *et al.*, 2006).

1.4.4 Soil

Chromium is present in most soils in its trivalent form, although chromium (VI) can occur under oxidizing conditions (ATSDR, 2008a). In the USA, the geometric mean concentration of total chromium was 37.0 mg/kg (range, 1.0–2000 mg/kg) based on 1319 samples collected in coterminous soils (ATSDR, 2000).

1.4.5 Food

There is little information available on chromium (VI) in food. Most of the chromium ingested with food is chromium (III) (EVM, 2002).

1.4.6 Smoking

Tobacco smoke contains chromium (VI), and indoor air polluted by cigarette smoke can contain hundreds of times the amount of chromium (VI) found in outdoor air.

1.5 Human exposure

1.5.1 Exposure of the general population

The general population residing in the vicinity of anthropogenic sources of chromium (VI) may be exposed through inhalation of ambient air or ingestion of contaminated drinking-water (ATSDR, 2000).

1.5.2 Occupational exposure

Inhalation of dusts, mists or fumes, and dermal contact with chromium-containing products are the main routes of occupational exposure. Industries and processes in which exposure to chromium (VI) occurs include: production, use and welding of chromium-containing metals and alloys (e.g. stainless steels, high-chromium steels); electroplating; production and use of chromium-containing compounds, such as pigments, paints (e.g. application in the aerospace industry and removal in construction and maritime industries), catalysts, chromic acid, tanning agents, and pesticides (OSHA, 2006).

Occupational exposures to several specific chromium compounds are reported in the previous *IARC Monograph* (IARC, 1990). With respect to chromium (VI) compounds, the most important exposures have been to sodium, potassium, calcium, and ammonium chromates and dichromates during chromate production; to chromium trioxide during chrome plating; to insoluble chromates of zinc and lead during pigment production and spray painting; to water-soluble alkaline chromates during steel smelting and welding; and, to other chromates during cement production and use (see Table 10; IARC, 1990, and OHCOW, 2005) for lists of occupations potentially exposed to chromium (VI)).

Estimates of the number of workers potentially exposed to chromium (VI) compounds have been developed by CAREX (CARcinogen EXposure) in Europe. Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX database estimates that 785692 workers were exposed to hexavalent chromium compounds in the European Union, with over 58% of workers employed in the following four industries: manufacture of fabricated metal products except machinery and equipment (n = 178329), manufacture of machinery except electrical (n = 114452), personal and household services (n = 85616), and manufacture of transport equipment (n = 82359). CAREX Canada (2011) estimates that 83000 Canadians are occupationally exposed to chromium (VI) compounds. Industries in which exposure occurred include: printing and support activities; architectural/structure metal manufacturing; agricultural, construction, mining machinery manufacturing; specialty trade contractors; boiler, tank, and container manufacturing; industrial machinery repair; auto repair; metalworking machinery manufacturing; steel product manufacturing; aluminum production; metal ore mining; coating, engraving, and heat treating. Welders were the largest occupational group exposed (n = 19100 men and 750 women).

Data on early occupational exposures to chromium (VI) are summarized in the previous *IARC Monograph* (IARC, 1990). Data from studies on chromium (VI) exposure published since the previous *IARC Monograph* are summarized below.

In a study to characterize occupational exposure to airborne particulate containing chromium, and to evaluate existing control technologies, the US National Institute for Occupational Safety and Health (NIOSH) conducted 21 field surveys during 1999–2001 in selected industries. Industries and operations